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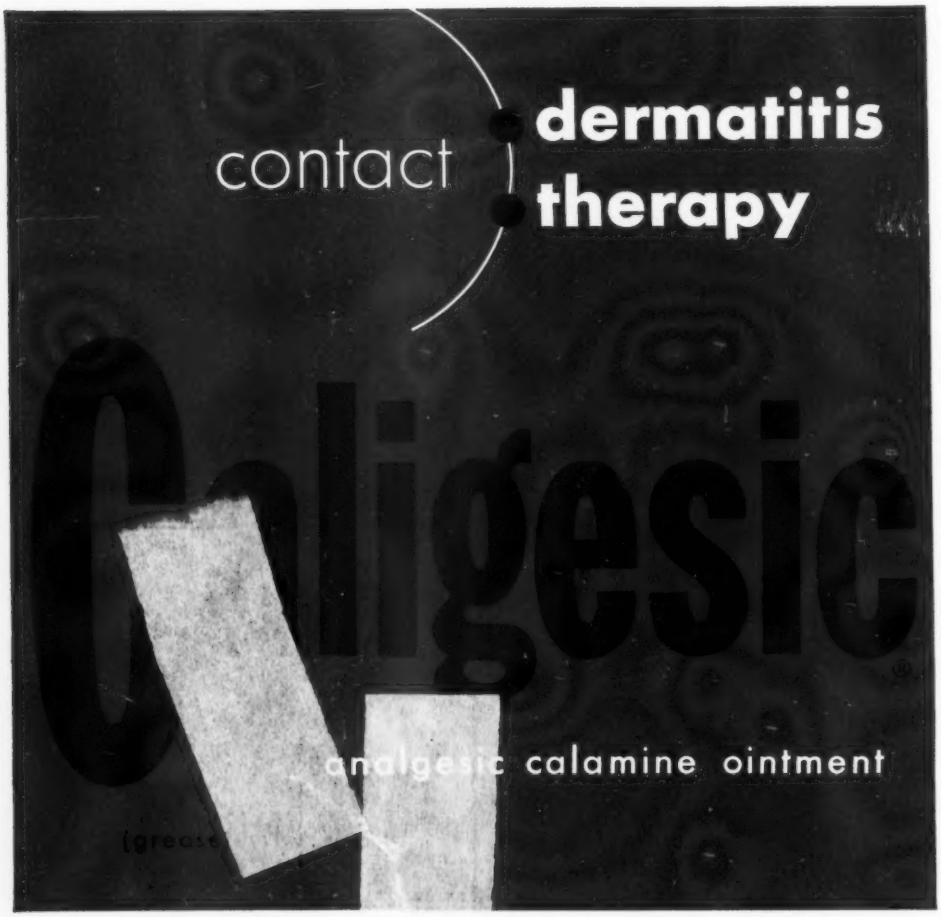

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This is a preliminary report on the surgical treatment of intractable asthma. While temporary dramatic relief has been obtained in severe cases of intractable asthma by unilateral left sided parasympathetic denervation and destruction of the pulmonary plexus, none of the cases in this series has been followed for a long enough period to predict the final outcome. Although final adoption of the surgical treatment of asthma must await extensive clinical and laboratory investigations, this report is published primarily to revive an interest in the subject.

The Surgical Treatment of Intractable Asthma

BRIAN BLADES*

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VARIOUS surgical procedures have been employed for bronchial asthma. Kummell[1] in 1923 operated upon the sympathetic nervous system for the treatment of asthma. Although he considered the vagus nerve supply as the chief motor innervation to the lung, he was fearful of the consequences of interfering with vagus fibers. Braeucker[2] who worked in Kummell's clinic had reported that stimulation of either the sympathetic or vagus systems might cause bronchial spasm. Accordingly, a unilateral cervical sympathectomy was performed in the hope that some of the motor fibers of the vagus entered the lung through the sympathetic system and would be destroyed. Kummell reported his original work with optimism, and interest was stimulated in the surgery of asthma throughout Europe.

Approximately a year after Kummell's original report, Kappis[3] was equally optimistic concerning the results of vagotomy for asthma. He severed the vagus on the right side below the level of the recurrent laryngeal nerve. Other surgeons have employed varying technics for operations on both the sympathetic and parasympathetic nerves to the lungs in an effort to alleviate bronchial asthma. Leriche[4,5] performed stellate ganglionectomy, and combined operations involving sympathectomy and unilateral vagotomy were employed by Kummell and others.

Although the sympathetic and parasympathetic systems have been the principal surgical targets, other organs have been altered or excised in attempts to cure asthma. For example, Freund[6] in 1906 removed varying numbers of costal cartilages in patients with asthma and emphysema. The principle of this operation was to increase respiratory excursion. Hirchberg[7] claimed to increase vital capacity of the emphysematous patient by transverse division of the sternum. Voelcher[8] advocated both paravertebral thoracoplasty and exeresis of intercostal nerves.

In addition to surgical procedures involving the chest, operations on the nose and throat, thyroid and even the spleen[9] are described in medical literature as beneficial in the treatment of intractable asthma.

SDB

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Research Grant from Medical Research and Development Board, Surgeon General's Office, U.S. Army.

BRIAN BLADES

The scholarly paper of Phillips and Scott[10] in 1929, on the surgical treatment of bronchial asthma, contains a review of the literature and a record of the various surgical procedures which have been tried and abandoned. They reported a case of intractable asthma in which the vagus nerve on the right was exposed, injected with novocaine, and the four main branches running to the posterior surface of the bronchi were divided. The main trunk of the vagus was freed and the nerve was cut at the inferior border of the right main bronchus. They state that sympathetic fibers were not identified but it seems likely that most of the sympathetic fibers involved in the posterior pulmonary plexus would have been destroyed. Their patient who considered life was unbearable before the operation, had absolute relief for three months. Even after exposure to horse dander to which he was extremely sensitive, he had only a mild attack of asthma and urged another patient to have the operation.

The next significant contribution to the surgery of bronchial asthma was made by Reinhoff and Gay[11-13] who in 1938 reported 11 cases of intractable asthma treated by bilateral posterior pulmonary plexus resections. Their approach to the problem resembles that of Kummell and Phillips and Scott and others who had operated upon the pulmonary plexus, except that bilateral intervention was routine. In 1942,[13] a summary of their results revealed that of 21 patients treated by bilateral resection of the pulmonary plexus, 8 report striking beneficial results, 9 died as the result of the operation or later, and 4 showed no improvement.

Modern contributions to the surgical treatment of asthma include the paper of Carr and Chandler[14] on the role of dorsal sympathetic ganglionectomy for intractable asthma. Carr has made a careful and conservative evaluation of 5 patients treated by this method, observed from four to ten years. All of his 5 patients have gained weight and have been able to work. Only two of the group have been away from their occupations because of asthma for a year's period. All respond to small amounts of medication when an attack of asthma is impending. Osler Abbott discussed Carr's paper and stated that he has employed bilateral operations on the parasympathetic system for intractable asthma. It is particularly interesting that Abbott has considered the most beneficial results to be in patients with emphysema.

A review of past and current literature indicates that original surgical interventions were directed toward the sympathetic system principally because alterations of the parasympathetic chains were considered prohibitively dangerous. There is probably no question that the dangers of excising the pulmonary plexus and interference with vagus nerves exceed those of operations on the sympathetic system. Anatomic and experimental evidence, however, indicate strongly that extirpation of the pulmonary plexus is a better method to eliminate or reduce extrinsic nerve stimuli.

It appears that practically all preliminary re-

ports on the surgical treatment of bronchial asthma are characterized by initial enthusiasm. The diversiform nature of asthma makes any therapeutic measure a potential temporary success. A classic example of honest optimism is contained in a paper by Phillips,[15] published in 1818, who reported that the simple application of galvanic current to the chest produced 20 or 30 cures of asthma.

Available data on the surgical treatment of asthma are insufficient to warrant conclusions concerning the future of justifiable surgical interventions for relief of this disease. It seems likely that early attempts may have been abandoned because of distressingly high operative mortality. Refinements in operative technics, and, more important, improvements in anesthesia should reduce greatly the immediate risks of operation. In this connection, it is interesting that nitrous oxide and cyclopropane have been employed as anesthetic agents for patients with asthma in the past. This is surprising since ether and avertin act as bronchial dilators and both experimental and clinical evidence indicate their use.

Another difficulty which has undoubtedly interfered with the study of asthma has been an inability to produce controlled bronchial spasm in experimental animals. Efforts in our own laboratory with histamine-produced bronchial spasm has not been applicable to the clinical problems.

There are several valid reasons to reinvestigate the possibilities of the surgical treatment of asthma. Most of the work on the subject was done during a period when simple exploration of the chest involved serious risks. The dramatic developments in the field of anesthesiology have greatly reduced these dangers. Even during the time when surgeons were handicapped by lack of both experience and equipment for working in the open chest, some gratifying results were reported. This may justify further endeavors in suitable cases, and finally the realization that certain cases in the field of psychosomatic medicine will require surgical rearrangement of the nervous system.

This preliminary report will not include a discussion of the various types of asthma. Whether extrinsic or intrinsic disease should have a bearing on a decision to recommend surgical treatment is apparently unknown. Warnings of the psychogenic factor appear often in the literature of the past. Precise evaluation is again impossible.

CASE REPORTS

Case 1—The patient, a 29-year-old white female was first seen in June 1947 at Walter Reed General Hospital. She was receiving oxygen and helium and appeared to be in a moribund condition. Adrenalin, aminophylline, morphine, and benadryl had been employed without benefit. Ether in oil and avertin were tried with no appreciable effect on the status asthmaticus and finally intravenous ether (50 cc. of ether in 1,000 cc. of saline, 100 mg. per kilogram of body weight) was employed. Some relief was obtained and the patient regained consciousness. Asthmatic wheezing continued but enough respiratory exchange was maintained to relieve cyanosis.

This patient had had bronchial asthma for fifteen years. For the past four years she was unable to live at home and was hospitalized on many occasions. During this four-year period she had 13 episodes of status asthmaticus severe enough to cause unconsciousness.

She was completely "adrenalin fast"; no benefit from the drug in controlling the disease had been noted for two years.

Complete and careful studies had been made concerning sensitivity to various agents. She was allergic to many things but particularly to house dust and cabbage. Attempts at desensitization had failed.

The situation was so desperate that surgical intervention was considered. Failure of sympathetic nerve blocks in other patients and perhaps the fact that adrenalin had no effect on this case resulted in the decision to alter the parasympathetic nervous system. For reasons unknown, the majority of recorded unilateral

operations on the vagus for asthma have been on the right side. On the basis that the arterial side of the chest might have a more abundant parasympathetic nerve supply, a left-sided approach was employed.

It is important to record that the patient was informed that the chance of success was small and that probably a second operation on the right side would be necessary.

Under avertin-ether anesthesia, a left posterolateral incision was made over the fifth rib. After division of the overlying muscles, a long segment of the fifth rib was resected subperiosteally. The pleura was incised and the left thoracic cavity exposed by means of rib-spreading retractors.

Alterations of the nerve supply consisted of the following steps: (1) identification of the left vagus nerve at the level of the pulmonary plexus; (2) the vagus was freed and retracted gently, but not cut; (3) the pulmonary plexus was destroyed; (4) all visible branches of the vagus to the pulmonary hilum and lung were divided; (5) esophageal branches and the main trunk of the vagus were preserved (esophageal branches become evident at about the level of the inferior pulmonary vein); (6) the sheaths of the great vessels, e.g., pulmonary artery and veins, were cleaned away as much as possible; (7) the pulmonary ligament was divided in order to destroy any fibers entering through it.

The chest wall was reconstructed in layers and the thorax closed without drainage after the lung was fully re-expanded.

During the first two weeks after the operation audible wheezes could be heard in the right lung. These were not evident on the left, but it is my opinion that this alteration of physical signs on the left resulted from the effects of an open thoracotomy and are therefore of no significance.

The patient's subsequent progress has been dramatic. She has had no attacks of asthma, does her own house work, eats cabbage, which she relishes, in great quantity and has gained 25 pounds. She has cooperated in trying to provoke attacks of asthma, particularly in connection with diet (cabbage) and contacts with house dust.

Case 2—A 37-year-old Negro male was admitted to the George Washington University Surgery Section of Gallinger Hospital. The patient had had asthma all his life. He moved from Georgia to the District of Columbia, hoping to find relief. This proved a vain hope.

Since 1937, it was unusual for him to have a day without wheezing and tightness in the chest. There was no seasonal distribution or specific allergen to be identified.

Hospitalization was required on approximately 20 occasions with a diagnosis of asthma and pneumonia. He had been given benadryl daily for about one year. Adrenalin had little effect on the attacks.

There is an additional and important feature in this case, namely, advanced emphysema associated with the asthma, and, in the opinion of Doctor Benjamin Manchester, cardiologist on the George Washington University Medical School Staff, cor pulmonalis.

An operation identical to that described in Case 1 was performed in July 1947. Shortly after induction of anesthesia, the patient stopped breathing spontaneously and it was necessary for the anesthesiologist, Doctor Lloyd H. Mousel, to maintain respiratory exchange for about four hours. Spontaneous respirations did not recur until approximately one hour after the operation was completed.

Emphysema of the left lung was so marked that the organ showed no sign of collapse when the thorax was opened. It is obvious that a combination of intractable asthma, emphysema, and cor pulmonalis made this subject a poor operative risk.

His condition remained serious for the first four postoperative days. It was not necessary, however, to give any medication for attacks of asthma. Following this critical period his condition improved rapidly and since July 1947 he has had no attacks of asthma, feels well, and enjoys full activity. Complete studies of the cardiac status before and after operation indi-

cate to Doctor Manchester that there has been marked improvement.

Cases 3 and 4 will not be discussed in detail. One patient, a young woman with intractable asthma of four years' duration, who for a year has received aminophylline almost daily, believes she has obtained beneficial results. As is the case with the other patients, postoperative observation has not been long enough to determine the final result.

Case 4 is of interest because of the peculiar but perhaps significant complicating factors. The patient, who is an inmate of St. Elizabeth's Hospital, has been under observation for an extended period with a diagnosis of schizophrenia. Since all students of asthma are interested in the role of psychogenic factors, this particular subject is, therefore, of significance.

This patient, a 35-year-old Negro, while under treatment for the psychiatric condition, had required almost daily medication for asthma since August 1947. After unilateral parasympathetic denervation and destruction of the pulmonary plexus, he has been free of symptoms and requires no medication.

SUMMARY

1. A preliminary report on the surgical treatment of intractable asthma is presented in the hope of reviving interest in the subject.

2. Surgical intervention should not be considered until conservative measures have failed completely.

3. All of the cases in this series have been followed for too short a period to predict the final outcome.

4. Temporary dramatic relief has been obtained in severe cases of intractable asthma by unilateral, left sided parasympathetic denervation and destruction of the pulmonary plexus.

5. Final adoption of the surgical treatment of asthma must await extensive clinical and laboratory investigations.

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Favorable and Unfavorable Results of Resection of the Vagus Nerves for Peptic Ulcer

WALTMAN WALTERS[1] AND HAROLD A. NEIBLING[2]

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LAST YEAR in speaking before the meeting of the Interstate Postgraduate Medical Association one of us (W. W.) considered some of the recent advances in the management of surgical lesions of the upper part of the abdomen.[1] At that time also rather brief reference was made to experience with resection of the vagus nerves or vagotomy in 21 cases of peptic ulceration. Operations in these 21 cases had been performed in the preceding eight months. In one of these cases a large recurring perforating gastric ulcer had developed after complete vagotomy and had produced symptoms which necessitated its removal by partial gastrectomy (Case 1, Table 1).

UNFAVORABLE RESULTS

Since that time recurring perforating craterous peptic ulcers have followed complete vagotomy or resection of the vagus nerves in 2 additional cases in our series (Cases 2 and 3, Table 1). This operation was performed in association with anterior gastroenterostomy and jejunojejunostomy in one case and with excision of the gastrojejunal ulcer, disconnection of the gastroenteric anastomosis, and pyloroplasty in the other. In the former case pain necessitated a second operation on August 15, 1947. A recurring anastomotic ulcer perforating into the abdominal wall was found and partial gastrectomy was carried out. The other patient who underwent resection of the vagus nerves on October 14, 1946, returned at our request for re-examination on August 24, 1947, at which time there was roentgenographic evidence of a recurring perforating duodenal ulcer with crater. The insulin test on August 26, 1947, gave negative results. In both of these cases the results of the Hollander[2] insulin tests were negative which, according to Dragstedt, is indicative of complete severance of the vagus nerves of the stomach.

In another case roentgenographic evidence of jejunitis was found four weeks subsequent to operation. This patient, however, did not have any recurrence of the ulcer symptoms which were severe before operation. The insulin test on this patient, likewise, gave negative results.

Three additional patients in our series (Table 2) continued to have distress of ulcer type for nine to ten months following their operations.

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Presented before the meeting of the Interstate Postgraduate Medical Association of North America, St. Louis, Missouri, October 14 to 17, 1947.

Results of insulin tests on 2 were negative and no insulin test had been done on the third. Roentgenographic studies on one did not give any evidence of ulceration and postoperative roentgenologic examinations were not made on the other 2.

The proved incidence of recurring ulceration, therefore, is 6 per cent in the 50 cases in which one of us (W. W.) carried out resection of the vagus nerves in the period from March 1946, to March 1, 1947, and symptoms of ulcer persisted in another 6 per cent.

The question has been raised whether the technic of the transabdominal resection of vagus nerves, which was used in these cases and in others which we have reported, has resulted in complete vagotomy. The answer is: If the Hollander insulin test is an indication of the completeness with which the vagus nerves in the stomach are resected, then complete vagotomy was accomplished in all 3 cases of proved recurring ulceration and in 2 of the 3 cases in which the symptoms of ulcer persisted, for in all 5 cases, results of insulin tests were negative. Moreover, the exposure of the lower part of the esophagus and the vagus nerves, which was obtained during the course of the operation of transabdominal resection of the vagus nerves, was good as was indicated by the motion picture which followed this presentation at the meeting.

WALTMAN WALTERS

Unfortunately recurring ulceration is not the only serious complication which follows the operation, for in studying the effects of the operation on the motility of the gastrointestinal tract, nine months after operation, we have found that 12 per cent of the patients have had persistent, troublesome symptoms, such as bloating, belching of foul-smelling gas, loss of appetite, and sometimes vomiting or diarrhea, a series of complications which have been most difficult to control. Some of these patients have complained bitterly of these symptoms. It was our hope that administration of urethane of beta-methylcholine chloride (urecholine) as a parasympathetic stimulant would be helpful in relieving the discomfort since Ruffin, Grimson, and Smith[3] have shown that it will increase the frequency and amplitude of waves of gastric peristalsis. Recently 4 of our patients who have severe early postoperative disturbance of motility received no benefit from the use of urethane of beta-methylcholine chloride. In all, results of insulin tests were negative. Our experience with this preparation in relieving the distress of the vagotomized atonic stomach has been disappointing.

That the operation is not without an immediate and possibly a future risk cannot be denied even though that risk is small. In one of our colleagues' cases in which resection of the vagus nerves and posterior gastroenterostomy were performed simultaneously in the treatment of a duodenal ulcer, persistent gastric retention with hypoproteinemia occurred. In spite of all efforts directed toward control of these factors the patient died on the fourteenth day after operation. At necropsy an unsuspected subdiaphragmatic abscess, the result

of perforation of the duodenal ulcer, was found. Resection of the vagus nerves apparently masked the symptoms of perforation in this case and may have done so in 2 of our cases in which recurring ulcers developed. In one of these cases pain occurred in the lower anterior portion of the thorax and the left upper part of the abdomen on motion, which probably was the result of the perforation of the gastrojejunal ulcer with its base on the abdominal wall. Moreover, in this case relief of distress by food and soda was not the same as that frequently noted in the presence of perforating gastrojejunal ulcer when vagotomy had not been performed. The other patient has had no pain typical of ulcer but has lost his appetite during the past three months (seven months after vagotomy, disconnection of the gastroenteric anastomosis, excision of a gastrojejunal ulcer, and pyloroplasty). The roentgenogram shows a recurring duodenal ulcer with a crater.

In speculating on causes of relief of pain referable to the ulcer immediately following vagotomy, we have called attention previously to the fact that the relief of pain was not due to the healing of the ulcer, first, because it could not heal in such a short time but also because, in 4 of our cases in which pain was relieved, roentgenographic examination from two and a half to three weeks after operation revealed persistence of the peptic ulceration.

During the first three months' period (March, April, and May 1946) in which one of us (W. W.) was performing transabdominal vagotomy, we were a little reluctant to accept the risk incurred in reducing the patient's blood sugar level to 40 mg. per 100 cc. or less by injections of insulin in order to determine whether the volume of gastric acids would increase. If increase occurs, the result of the test is considered positive and a positive reaction indicates that all of the branches of the vagus nerves to the stomach had not been cut. After the problem was discussed with one of our surgical friends from another clinic, who assured us that he had carried out the procedure in many cases without risk, we began using it as a routine procedure approximately ten to fourteen days after vagotomy if the patient's general condition permitted. Therefore, from that time on we have obtained insulin tests in 39 out of 40 cases. A study of these insulin tests discloses that in 67 per cent of the cases negative results were obtained. These negative results indicate that all branches of the vagus nerves to the stomach had been resected. In 33 per cent of the 40 cases, however, the tests gave positive results. In both groups we have studied the response to resection of the vagus nerves alone and in combination with other operations on the stomach with regard to (1) relief of symptoms of ulcer, (2) reduction of gastric acidity, and (3) the incidence of motility disturbances producing troublesome symptoms.

In the cases in which results of the insulin tests were positive, a greater reduction of gastric acidity occurred and achlorhydria developed in a greater percentage than in the cases in which insulin tests were negative. These figures were 93 per cent and 69 per cent, respectively. The incidence of troublesome disturbances of motility were about equal in the two groups. The most striking observation, however, is the fact that nearly all recurrences of ulceration took place in the group of cases in which the results of insulin tests were negative, a circumstance which we are unable to explain.

In trying to explain the difference in these results with those reported by Dragstedt[4] and his associates, we have compared the relative incidence in which the operation was performed for duodenal ulcer, gastrojejunal ulcer, and gastric ulcer by ourselves, by Ruffin, Grimson, and Smith[3] from Duke University, by Moore and his associates[5] from the Massachusetts General Hospital, and by Colp[6] from Mount Sinai Hospital, New York. Eighty-six per cent of Dragstedt's patients had duodenal ulcer and 9 per cent had gastrojejunal ulcer. In our series, 68 per cent (34 patients) had duodenal ulcer and 14 per cent had gastrojejunal ulcer. If the 68 cases in which operations on the vagus nerves were performed by other surgeons at the Mayo Clinic are added, the percentages are

TABLE 1

DEFINITE RECURRENCE OF ULCER AFTER VAGOTOMY

Case	Ulcer and Time of Vagotomy	Associated Operation	Result of Insulin Test	Postoperative Symptoms	Postoperative Roentgenologic Diagnosis and Date	Treatment
1	Gastric ulcer 7-29-46	Excision of ulcer	Negative	Ulcer distress	Penetrating gastric ulcer 12-18-46	Medical management unsuccessful; high gastric resection 1-13-47 for penetrating gastric ulcer
2	Duodenal ulcer 8-26-46	Anterior gastroenterostomy with subsequent jejunojejunostomy	Negative	Atypical ulcer distress	Negative; gastroscopic positive for ulcer 8-1-47	Take down gastroenteric stoma; resection of stomach 8-15-47 for anterior penetrating gastrojejunal ulcer
3	Gastrojejunal ulcer 10-14-46	Removal of gastroenteric stoma, excision of ulcer and pyloroplasty	Negative	Poor appetite; moderate distress	Duodenal ulcer with crater 8-27-47	Medical management

65 for duodenal ulcer and 29 for gastrojejunal ulcer. It is interesting to note that the percentage of patients operated on for duodenal ulcer and gastrojejunal ulcer reported by the others referred to, except Dragstedt, practically parallel those of the Mayo Clinic series (Table 3).

Resection of the vagus nerves without associated operation on the stomach was done in only 17 of our 50 cases and in 31 of the 68 cases of our colleagues at the clinic. In 10 cases of our group the operation was performed for duodenal ulcer. The reason for the small number of cases of duodenal ulcer in which this operation alone was carried out was that in the other cases of duodenal ulcer the ulcer was so large and seemed to be of such an obstructive or potentially obstructive nature that some type of drainage operation of the stomach, such as gastroenterostomy, and in a few cases, gastric resection was thought advisable and in cases of gastrojejunal ulcer it was considered worth while in most cases to remove the gastrojejunal ulcer and disconnect the gastroenteric anastomosis at the time of vagotomy. In 2 cases the gastrojejunal ulcer was not removed and the gastroenteric anastomosis was not disconnected.

In 87 per cent of the cases of duodenal ulcer at the Mayo Clinic medical treatment has been employed in recent years. In the complicated cases of duodenal ulcer in which operation has been performed, partial gastrectomy with partial duodenectomy has been the operation of choice. Resection of the vagus nerves has been performed in some cases of this type, in cases of gastrojejunal ulcer, and gastric ulcer.

If resection of the vagus nerves were employed in more duodenal ulcer cases in which the lesion is now treated medically, results of this operation might be expected to be better than they have proved in our series.

Small*,[7] one of my assistants, has made an intensive review of the literature relating to the effects of vagotomy in animals and the clinical results of patients with peptic ulceration. Time does not permit more than the briefest reference to these historical data. However, neither those working on the problem experimentally nor those working on it clinically to the time Dragstedt's contribution was made were able to demonstrate to Small's satisfaction that a decisive viewpoint could be reached regarding results of the procedure in animals or patients.

One of the interesting contributions, in our

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TABLE 2

SUSPECTED RECURRENCES OF ULCER NOT CONFIRMED BY ROENTGENOLOGIC EXAMINATION

Case	Type of Ulcer and Date of Vagotomy	Associated Operation	Result of Insulin Test	Postoperative Symptoms
4	Duodenal ulcer 10-31-46	Posterior gastro-enterostomy	Negative	Ulcer distress; fullness; vomiting; loss of weight
5	Gastric ulcer and gastritis 9-27-46	Gastrotomy	Negative	Ulcer distress gradually diminishing; occasional vomiting
6	Duodenal ulcer 6-6-46	Anterior gastro-enterostomy	None	Ulcer distress

TABLE 3

COMPARATIVE STATISTICS OF REPORTED VAGOTOMIES

		Duodenal Ulcer		Gastrojejunal Ulcer		Gastric Ulcer	
	Cases	Cases	Per Cent	Cases	Per Cent	Cases	Per Cent
Dragstedt	170	147	86	15	9	8	5
Mayo Clinic Our series	50	34	68	7	14	9	18
Total series	118	77	65	34	29	7	6
Grimson	57	40	70	10	18	7	12
Moore	74	57	77	16	22	1	1
Colp	33	20	61	12	36	1	3

opinion, indicating that results of vagotomy might be transitory, was that of Hartzell[8] and Vanzant[9] who showed that from six months to two years after resection of the vagus nerves of the stomach of dogs, gastric acidity and motility returned to normal. The recent clinical reports of Moore and associates indicate that the same recur in some human beings.

INDICATIONS FOR RESECTION OF THE VAGUS NERVES

The greatest field of usefulness for resection of the vagus nerves seems to be in the treatment of ulceration after partial gastrectomy. Recently Priestley[10] has reported on a collected series of 16 cases of ulceration after partial gastrectomy for which vagotomy was performed at the Mayo Clinic. Results were good in 12, fair in 3, and poor in 1 case. In the same study in 21 cases of gastrojejunal ulcer after gastroenterostomy good results have followed resection of the vagus nerves in 19 cases, fair results in 2 and poor results in none. Despite these figures we are inclined to look with skepticism at this time on the chance that healing of all gastrojejunal ulcers developing after gastroenterostomy will result from resection of the vagus nerves alone. The reason for this skepticism is a case which we have mentioned previously. In this case a perforating gastrojejunal ulcer developed and required partial gastrectomy approximately ten months after anterior gastroenterostomy, resection of the vagus nerves, and subsequent jejunojejunostomy (Table 1). The result of the insulin test was negative in this case.

Resection of the vagus nerves has so far seemed to have merit in cases in which dyspepsia caused by chronic duodenal ulcer does not respond to a medical regimen and the duodenal ulcer at operation is found to be small and not obstructive and other operations are not necessary on the stomach. In the 10 cases of our series in which this type of lesion was present resection of the vagus nerves has relieved the pain of ulcer at the expense, however, of dilation of the stomach with troublesome symptoms of disturbances of motility in 3. When resection of the vagus nerves was combined with other operations, such as gastroenterostomy, as it was in 24 cases of duodenal ulcer in our series, no improvement in the results is evident over those which experience of many years in many cases has shown occurs when gastroenterostomy or some other opera-

tion is performed without vagotomy. Although relief of ulcer distress occurred in 22 of our 24 cases, recurring ulceration necessitated gastric resection in 1 and troublesome disturbances of motility were present for at least nine months in 6 cases.

Resection of the vagus nerves has no place in the treatment of chronic gastric ulcer if the ulcer can be removed in the course of partial gastrectomy. In 9 of our 50 cases resection of the vagus nerves was done for gastric ulcer. Recurrence of ulcer took place in 1 case and disturbances of gastric motility persisted for seven months or longer in 3.

Experience and time will be required to tell just what place resection of the vagus nerves has in the treatment of duodenal and gastrojejunal ulceration.

In 1946, resection of the stomach for gastric ulcer was performed in 101 cases with a mortality rate of 2.0 per cent. In the same year gastric resection for duodenal ulcer was done in 296 cases with a mortality rate of 2.0 per cent. In view of the low mortality rate and good results in these cases, resection of the stomach and not resection of the vagus nerves seems on the whole to be the operation of choice for both duodenal and gastric ulcers.

SUMMARY OF RESULTS IN OUR SERIES

Resection of vagus nerves alone—In our series of 50 cases to date vagotomy alone was done without other procedure in 10 for duodenal ulcer, in 2 for gastrojejunal ulcer, and in 5 for gastric ulcer. All of the patients obtained relief of the pain caused by ulcer. In 3 cases of duodenal ulcer and in 1 of gastric ulcer disturbances of motility occurred after vagotomy. In one case of duodenal ulcer and one of gastric ulcer the results of one insulin test in each case after operation were positive and in neither case was gastric acidity reduced. Four of the patients with duodenal ulcer were reported at dismissal (approximately two and a half to three weeks after operation) as still having visible ulcers on roentgenologic examination. Two of these patients gave a positive reaction to the insulin test.

Resection of vagus nerves and other gastric operations—Vagotomy with a simultaneous gastric operation was performed in 24 cases of duodenal ulcer, in 5 of gastrojejunal ulcer, and in 4 of gastric ulcer. In 22 of the 24 cases of duodenal ulcer, in 4 of the 5 cases of gastrojejunal ulcer, and in 2 of the 4 cases of gastric ulcer, relief of distress from the ulcer was obtained. Ulceration recurred in one case of gastric ulcer and in one case of duodenal ulcer and subtotal gastrectomy was necessary six and ten months later. The gastric ulcer failed to heal in another case, and in one case a duodenal ulcer recurred after excision of a gastrojejunal ulcer. In all, gastric acidity was reduced and reactions to the insulin test after vagotomy were negative. In 6 cases of duodenal ulcer for which vagotomy and associated gastroenterostomy were carried out, in 2 cases of gastrojejunal ulcer, and in 3 cases of gastric ulcer, moderate to marked disturbances of motility developed. Of these, one of the patients with duodenal ulcer who reacted negatively to the insulin test and one patient with gastrojejunal ulcer who reacted positively to the insulin test had no reduction in gastric acidity after operation.

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Recent Laboratory Methods and Their Interpretation

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THE diagnosis of disease has been notably assisted in the last quarter of a century by remarkable developments in laboratory methods. The purpose of this discussion is to point out some of the outstanding advances.

The diagnosis of early carcinoma is one of the most important advances. It is carried out by examination of vaginal smears to pick up early cases of carcinoma of the uterus, by the study of malignant cells in sputum and bronchial secretions in the diagnosis of bronchogenic carcinoma, and by the examination of centrifuged urinary sediment in the diagnosis of malignant lesions of the urinary tract. This means of diagnosis is primarily based on the epic-making work of Papanicolaou and Traut. Many other workers have since followed their first steps.

The diagnosis of uterine carcinoma, utilizing these methods, has materially advanced; these methods are also applicable to large-scale operations or screening. In other words, if these methods are applied to vaginal secretions of every woman in a large clinical service, a number of cases will be picked up before clinical symptoms or biopsy results would have proved the condition. These methods as applied to vaginal smears are by no means intended to supplant biopsy technic, but are used as an adjunct to it.

The staining procedure consists of fixing smears in a mixture of equal parts of 95 per cent alcohol and ether for five to fifteen minutes. When slides are to be sent to a hospital laboratory for staining, a drop or two of glycerin between two fixed slides provides very adequate protection for shipment. Rinse successively in 70 and 50 per cent alcohol and distilled water and then stain in Harris hematoxylin for two to six minutes. Decolorize by rapid immersion into a 0.5 per cent aqueous hydrochloric acid solution. The intensity of the color depends on how many times the slide is immersed in alcohol. Depth of color must be checked microscopically. The slide is placed in running water for five minutes and finally rinsed in distilled water. The preparation is then passed successively through 50, 70, 80, and 95 per cent alcohol. For rapid preparation a single 70 per cent alcohol bath may replace the above graded series. The slide is now stained for one minute in OG-6, which is a single Orange G stain. The counter-stained slide is now rinsed five to ten times in each of

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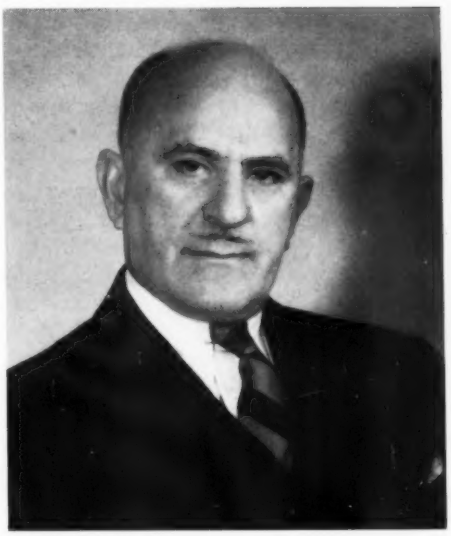
two jars containing 95 per cent alcohol. It is then placed in EA-50 for two minutes. EA-50 is a multiple polychrome stain.* Rinse the preparation five to ten times in each of three jars containing fresh 95 per cent alcohol. Transfer to absolute alcohol and xylol and mount in clarite, Canada balsam, or gum dammar.

In order to attain proficiency in this method of diagnosis, pathologists must learn the normal appearance of vaginal smears by studying the various cells associated with hyperplasia, endometritis, and normal postpartum. They must learn to recognize carcinomatous cells from cervix and endometrium. In other words, it requires a thorough study of cytology to become proficient in evaluating the findings.

In addition to uterine carcinoma, splendid work has been done in the detection of bronchogenic carcinoma by microscopic examination of sputum and bronchial secretions. The work of Woolner and McDonald of the Mayo Clinic is notable in this regard. Their technic differs slightly from that of Papanicolaou. These workers found malignant cells in the sputum or in bronchial secretions where tumors involved the hilar regions. Whether or not typical cells can be found in sputum depends on whether a direct connection can be traced between the tumor and the main bronchial tree. It is necessary to recognize the normal epithelial cells found in this material, including squamous cells which line the mouth and pharynx and ciliated columnar cells which line the trachea and bronchi. They divide these bronchogenic carcinomas into three groups: (1) undifferentiated or anaplastic carcinoma, (2) squamous cell carcinoma, and (3) adenocarcinoma.



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ANOTHER important advance in the diagnosis of malignancy is by means of microscopic examination of urinary sediment. This has been covered by another contribution from the Mayo Clinic, namely, the work of Daut and McDonald. Their method consists of collecting the urine in 95 per cent alcohol, centrifuging, decanting, and placing a drop of the sediment on a slide with a pipette, drying the smear, and staining with Papanicolaou's staining methods. Also, sediment may be stained with methylene blue and fat may be stained with Sudan IV.

Cytologic diagnosis of malignant processes, according to these workers, is based on (1) the nucleus (size, anisonucleosis, poikilonucleosis, hyperchromatosis, fragmentation, multiplicity); (2) the nucleolus (multiplicity, variations of size, hyperchromatosis), and (3) the cytoplasm (fat-filled, basophilic reaction). This procedure is quite useful for screening all unexplained gross and microscopic hematurias, questionable renal masses, or questionable lesions of the renal pelvis or calices as seen in excretory urography.

These workers also point to another very important application of this method, namely, the detection of carcinoma of the prostate gland before such a lesion is palpable in the rectum or before erosion into the urethra has occurred.

*OG-6 and EA-50 are available in bottles of 100 cc. prepared by the Gradwohl Laboratories, 3514 Lucas Ave., St. Louis 3, Mo.

The test offers no guide to the extent of invasiveness of the tumor. There is no way of grading the tumor nor of determining the point of origin of the malignant cells. Possibility of error may be present but the advantages outweigh the disadvantages.

The treatment of infections with penicillin and streptomycin has now advanced to the point where it is an everyday procedure. In order to obtain the best possible results in administrating these antibiotics, dosage should be controlled by estimation of the penicillin and streptomycin level of the blood by laboratory methods. It is foolhardy to believe that these drugs may be successfully administered without this control.

ANOTHER very interesting advance in the last few years is the diagnosis of pregnancy. The generally accepted test is the Aschheim-Zondek test, using immature, female mice, based on the principle of the production of corpora hemorrhagica caused by gonadotropic hormones in urine. This gives, according to most reports, 98 to 99 per cent accurate results.

A modification of this method is that by Friedman, in which isolated mature female rabbits are used with the production of corpora hemorrhagica caused by gonadotropic hormones in urine, very similar to results obtained by the Aschheim-Zondek test. This requires twenty-four to forty-eight hours and gives an all-or-none response. It is 98 to 99 per cent accurate.

The latest method which has attracted attention is that using the *Xenopus laevis* mature female (clawed toad). This is based on the external extrusion of eggs caused by gonadotropic hormones. It may be finished in from four to twelve hours by concentration of urine, and is from 98 to 100 per cent accurate. It is preferable to the other methods because of the short time required to perform the test, its simplicity, and its economy since many tests can be made from each toad. It calls for a single subcutaneous injection, and requires no special precautions. The end reaction is the simple observation of eggs in the water. Compared with this, the Aschheim-Zondek test requires ninety-six hours, operation, five fresh mice for each test, feeding and cleaning problem, multiple injections (forty altogether), animals must be killed, and the ovaries must be searched for in 5 animals.

The Friedman test requires thirty-six to forty-eight hours, necessitates operation, requires intravenous injection (usually two), and the rabbit is usually killed. In addition, the rabbit must be isolated and the search for ovaries carried out.

Probably the most interesting and important advance that has been made recently is that concerning the Rh blood factor. This is a phenomenon based on numerous facts connected with isoimmunization, which means immunization of a member of a species by yet another member of the same species. The discovery of the Rh factor has done much to explain many untoward transfusion reactions commonly called hemolytic reactions. Landsteiner and Wiener deserve great credit for their discovery of the Rh factor and an explanation of its reactions in retransfusions.

Landsteiner and Wiener in 1937 detected the presence in the blood of monkeys a factor which they subsequently called Rh. In using animal blood instead of human blood for preparing antisera they discovered that some of their antisera for rhesus monkey blood contained an agglutinin reacting with the blood cells of 85 per cent of the white population, quite independently of the blood groups or M, N, and P factors. In 1939 Peters and Wiener found 3 cases of hemolysis following transfusions of blood of the homologous groups, which were proved to be due to isoimmunization to the rhesus factor. Thus, this new blood factor became clinically very important and cases were reported. Wiener stated in his Alvarenga Prize lecture that this was the reason why the Rh factor, found by Landsteiner and Wiener in 1937, was first announced in January 1940. Briefly, the blood cells of 85 per cent of all white individuals are agglutinated by the anti-rhesus sera, and these contain the Rh ag-

glutinogen. Such individuals are called Rh positive, while the remaining 15 per cent are called Rh negative.

In connection with blood transfusion, Wiener demonstrated that the Rh agglutinogen is antigenic to man. Thus, while Rh negative individuals can be safely transfused with Rh positive blood, they may become sensitized to the Rh factor as a result of the transfusion, and cannot again safely receive Rh positive blood. Therefore, it is preferable to transfuse Rh negative individuals with Rh negative blood. Preferably, use ORh negative blood or Rh negative blood compatible with the special blood group of the recipient. It has been properly recommended that all females, no matter at what age they require transfusions, be Rh tested, even though it is the first transfusion. If they are Rh negative and are transfused with Rh positive blood, they may develop some degree of anti-Rh antibodies. These qualities may persist for an indefinite period so if another transfusion is required and Rh positive blood is used, severe transfusion reactions may occur. It must also be kept in mind that these Rh negative females, who have been transfused at some time in early life with Rh positive blood, are isoimmunized to the Rh factor; when undertaking marriage and becoming pregnant, if the fetus is Rh positive, they will most certainly have severe intragroup transfusion reactions. If the fetus is Rh positive their chances of bearing normal infants are practically nonexistent.

The Rh types are hereditarily determined, the Rh factor being transmitted as a single Mendelian dominant by a pair of allelic genes, Rh and rh. Since every individual possesses a pair of genes from every series of allelic genes, one being derived from the mother, and the other from the father, there are three genotypes possible. Rh negative individuals are always homozygous; Rh positive individuals may be either homozygous or heterozygous. Therefore, two Rh negative parents can have only Rh negative children. If one parent is Rh negative, and the other is Rh positive, the children will all be Rh positive if the Rh positive parent is homozygous. If the Rh positive parent is heterozygous, there is equal chance that the children may be Rh positive or Rh negative; or, as it is usually stated, one-half of the children will be Rh positive and one-half will be Rh negative. When both parents are Rh positive, all the children will be Rh positive, except when the parents are both heterozygous, in which case one-fourth of the children will be Rh negative.

Rh negative individuals may become sensitized to Rh antigen in one of two ways: (1) sensitization may result from a transfusion of Rh positive blood, or (2) in women, sensitization may result from pregnancy with an Rh positive fetus. Sensitization by either of these methods may result in a serious hemolytic reaction if transfusion with Rh positive blood is given. Therefore, all Rh negative women who are to be transfused must be given only Rh negative blood.

Levine in 1940 noted that sera of patients who had had repeated miscarriages or abortions contained atypical isoagglutinins related to the Rh factor. In 1941 Katzin found that the serum of the patient previously described by Levine and Stetson agglutinated the same cells as the newly discovered anti-rhesus rabbit serum. Levine, Katzin, and Burnham called attention to the fact that a diagnosis of erythroblastosis fetalis had been made on some dead fetuses which came from the union of Rh positive and Rh negative parents. Vogel noted the majority of the mothers had Rh negative blood.

It is plausible, therefore, to accept the doctrine that Rh positive fetal cells entering the maternal blood stimulate the formation of anti-Rh agglutinins; such agglutinins, passing back to the fetus, agglutinate and destroy the fetal erythrocytes. The only barrier between the fetus and the mother is the fragile wall of the placental villus. Normally the blood of the child circulates inside the villus, while the maternal blood circulates outside this delicate structure. Osmosis may occur through this wall. The placenta is extremely susceptible to the ef-

fects of tumors, trauma, and disease. Therefore, trauma, which is seen later in scars of the placenta, permits hemorrhage of fetal blood cells into the maternal circulation. In this way, they are carried into the uterine veins and into the general circulation of the mother, constituting the mechanics of transfer of blood cells between fetus and mother.

It is believed that the mating of Rh negative women with Rh positive husbands, occurring once in 10 marriages, results in congenital hemolytic disease because of the phenomena already explained. About one in 25 Rh negative women become sensitized when bearing an Rh positive fetus. The first child is rarely affected, because it takes at least one pregnancy and sometimes more before a sufficient degree of sensitization develops. In most cases where the first-born was affected, a careful history revealed that the women had previously received a transfusion of Rh positive blood.

Summarizing the facts relating to the Rh factor:

1. *In retransfusions*—If the recipient is Rh negative and the donor is Rh positive, the Rh agglutinogen in the donor's blood cells acts as an antigen and stimulates the formation of anti-Rh agglutinins and hemolysins in the patient's serum. The patient is now isoimmunized to the Rh factor. If this patient is again transfused with Rh positive blood cells, the anti-Rh antibodies, which result from the first transfusion, then agglutinate or hemolyze the incoming donor cells, resulting in a transfusion reaction or death. Therefore, always use Rh negative donor blood in retransfusions into Rh negative recipients.

2. *In primary transfusions of pregnant and postpartum women*—With an Rh negative mother and an Rh positive father, the fetus will probably be Rh positive. Through osmosis, or traumatic placental leaks, Rh positive fetal blood seeps into the mother's circulation, causing the mother to form anti-Rh antibodies in her blood serum. She is now isoimmunized to the Rh factor. If this woman is given a transfusion with Rh positive blood, the anti-Rh antibodies now present in her blood plasma react with the incoming donor blood cells and agglutinate them or hemolyze them, or both, resulting in a transfusion reaction or death. Therefore, always transfuse Rh negative pregnant or postpartum women with Rh negative blood.

3. *In erythroblastosis fetalis*—The fetus will most likely be Rh positive if the mother is Rh negative and the father is Rh positive. Through seepage of blood into the maternal circulation, the mother's blood forms anti-Rh antibodies. Through imperfections in the placenta, the mother's blood now re-enters the fetal circulation, hemolyzes and agglutinates the Rh positive cells, and also attacks the hematopoietic system. As a result, the fetus is either expelled as an abortion, is macerated, is stillborn, or, if born alive, is erythroblastotic. If the infant is transfused with Rh positive blood cells, the anti-Rh antibodies in the infant's blood, derived from the mother, react with the incoming Rh positive donor blood cells. If the infant is transfused with blood from the mother, the anti-Rh antibodies, present in the mother's blood as a result of isoimmunization, attack the Rh positive blood cells of the infant, causing a transfusion reaction or death of the infant. The transfusions to be carried out in erythroblastotic infants should always utilize Rh negative blood.

The present tendency, therefore, in regard to safe blood transfusion, is to investigate all bloods for the Rh factor. In the primary examination of pregnant women, the practitioner must investigate the bloods of both parents with the idea of estimating isoimmunization with resultant disturbances in the child or possible death of the fetus. Some likelihood of the degree of the isoimmunization may be ascertained, assuming the mother is Rh negative and the father is Rh positive, if estimation of the anti-Rh qualities of the mother's blood is made during pregnancy.

There are various methods of determining the Rh factor, using both test tube and slide methods. Reliable testing sera are on the mar-

ket and most laboratories are equipped to make these tests with exactitude and punctuality.

TREMENDOUS interest has been aroused in this country in connection with the laboratory diagnosis of tropical medical and parasitologic cases. World War II is largely responsible for this. We projected out frontiers all over the world and our Service personnel came in contact with many diseases hitherto not seen by American physicians. Our Army and Navy medical personnel had unusual opportunities to become proficient in the study of these diseases. Many of these cases returned to our shores, some still remain under military medical supervision, others have been released to become the subjects of study of civilian physicians. Rapid transportation by air, too, has been a means of conveying to the United States diseases hitherto not seen.

It is necessary at this time to emphasize the importance of carrying out blood and stool examinations of many patients. The use of concentrated methods offers us an opportunity of obtaining a high percentage of accurate diagnoses. The thick drop of blood hemolyzed and stained with Giemsa stain is a concentrated method for investigation of the plasmodia of malaria, trypanosoma, leishmania, spirocheta of relapsing fever, microfilaria, etc. There are many concentration methods to aid in the search for eggs, larvae, and cysts. All are based on the use of a large amount of fecal material which is rendered homogeneous with water or saline solutions and screened. Cysts, eggs, and fine forms pass through the screen and are collected and centrifuged. They can then be found in the sediment.

Many concentration methods are carried out with solutions of a density below that of the eggs and cysts—Telemann and its modifications, method of Carles and Barthelemy, etc.—concentrating the eggs and cysts at the bottom of the tube. Others use solutions of a higher density than that of the eggs, the superficial portion of the fluid then being examined.

The various methods commonly used are (1) the method of Fuelleborn, (2) the method of Telemann, which is suitable for all eggs, (3) the acetic acid and ether concentration method, (4) the Tulane method of concentration worked out by Faust, Tobie, and others. This embodies the dilution of feces in 10 parts of water strained through wet cheesecloth, centrifugalization, pouring off of supernatant fluid, adding water, centrifuging again, adding 3 to 4 cc. of a solution of zinc sulfate with a specific gravity of 1.180, shaking, centrifuging, and using the top portion for examination. (5) Baroody's modification of the Faust method for concentration of cysts and ova is also advantageous. His method differs from that of Faust in that he uses larger amounts of stool and in this way succeeds in finding cysts and eggs where one fails to do so with the original Faust method. His modified technic is a combination of Baroody and Most's centrifugal sedimentation method.

In this modification, 10 gm. of feces are placed in a 125 cc. Erlenmeyer flask containing about 75 cc. of warm water (about 40° C.); stopper the flask and shake until emulsified.

Strain through a layer of wet gauze into a 50 cc. centrifuge tube (teated bottom).

Centrifuge for one minute at 2,500 r.p.m. and pour off supernatant fluid. Add warm water to the sediment from a regulated faucet (force of the water will disperse the fecal particles and cleanse them) and centrifuge again at the same time and speed. Decant supernatant fluid; repeat one more washing and centrifugation; again decant supernatant fluid.

Add about 10 cc. of warm water and agitate sediment by shaking; then pour quickly all of contents into a 15 cc. centrifuge tube. Centrifuge for one minute at 2,500 r.p.m. and decant supernatant fluid.

Add about 10 cc. of zinc sulfate solution (33 per cent, specific gravity 1.180) to the sediment and stir with applicator sticks. Add zinc sulfate nearly to top of tube. Centrifuge for one minute at 2,500 r.p.m. Ova and cysts will float to the surface.

Take several loopfuls (bacteriologic loop) from surface and place on slide; add 1 drop of

D'Antoni's or Lugol's iodine and cover with a cover slip. Examine for ova of helminths and cysts of protozoa under low-power objective of microscope.

IT WILL be noted that in this method a much larger sample of feces is utilized, thereby increasing the possibility of detection in lightly infested cases or if cysts and ova are rare in the stool. Cysts may exist in "packets" and can be missed from a remote small section. Secondly, the use of warm water (about 40° C.) has advantages over the use of regular or so-called cold water. The use of warm water eliminates a high percentage of the scum which has been observed when cold water was used.

Baroody and Most worked out what, in our opinion, is the best method for finding *Schistosoma japonicum* eggs, as follows:

1. Place from 10 to 15 gm. of the feces in a 125 cc. Erlenmeyer flask containing about 100 cc. of lukewarm tap water. Insert a No. 4 rubber stopper and shake vigorously for one or two minutes, or until the particles are in fine suspension.

2. Strain the emulsified feces through two layers of wet gauze into a 50 cc. centrifuge with teated bottom (tube dimensions: height, 4¾ inches; diameter, 1 inch).

3. Centrifuge at 1,500 r.p.m. for thirty seconds (brake of centrifuge applied gradually).

4. The supernatant fluid is decanted and tap water of about 40° C. is added to the 50 cc. mark. Insert a rubber stopper and shake several times until the sediment is finely dispersed. The warm water causes a scum to rise to the surface. This is desirable.

5. Repeat procedures 3 and 4 until the supernatant fluid is clear; three washings and three centrifugations are usually sufficient.

6. After the last washing and centrifugation the clear supernatant fluid is poured off and the packed sediment remains. If the finger is gently tapped against the side of the tube, the packed sediment is dispersed and settles to the bottom of the tube by gravity within a minute.

7. With a rubber-bulbed pipette, place 4 drops of mixed sediment on a glass slide and cover with a large cover slip size 22 by 50 mm. Make at least two slides.

8. Examine under low-power objective of the microscope for eggs of schistosoma. *S. japonicum* eggs are oval, 70 to 100 by 50 to 60 microns, may or may not have a rudimentary spine, and in blue-white light appear greenish orange. *Schistosoma mansoni* eggs are elongated, 114 to 175 by 45 to 68 microns, and have large lateral spines. In both species, if the ova are visible, the miracidia will exhibit movements within the eggshells, and the activity of the flame cells may be seen under higher magnification.

9. If the slides are negative for schistosoma ova, add about 10 drops of water to the remaining sediment in the tube, leave overnight in a warm place, and examine the following day for miracidia. The entire contents of the tube can be placed on a large slide and examined under a dissecting microscope. This phase of the examination takes less than two minutes.

10. Excluding procedure 9, not more than five minutes are required for the examination of each slide, and not more than from fifteen to twenty minutes are required for procedures 1 through 8.

Summary of the method—(1) A large sample of the feces is used; this is especially valuable in light infections; (2) viability of the ova is determined; (3) rapidity of method—report can be rendered within fifteen minutes; (4) a hatching test is part of the method; (5) other ova, cysts of protozoa, and larvae of helminths may also be found and identified (for protozoan cysts, add a drop of Lugol's or D'Antoni's iodine to slide); (6) preserved concentrated specimens can be made quickly by adding 10 per cent formalin to the sediment in the tube at the end of the fresh examination; (7) no chemical reagents are required; minimum standard laboratory equipment is used.

Baroody and Most compared the direct smear examination and their water centrifugal sedimentation method by examining 1,026 consecutive fecal specimens simultaneously. These patients had all received treatment previously

and were under observation for the evaluation of the success or failure of various forms of therapy. They found 10 patients positive by direct examination of fecal material free of grossly visible blood or mucus. Positive results also were obtained in water centrifugal flotation. In addition, 39 patients were found positive by the latter method or a relative efficiency of 4.9 to 1 for this method compared to direct smear examination. Such patients, having all been Army personnel diagnosed overseas or in this country, had received one or more courses of treatment. Therefore, by direct smear examination the infection would not have been detected if no mucus or blood were present in the stools. Conditions of this test naturally would simulate those faced by physicians and laboratories in civil or veterans' facility practice.

As compared with the zinc sulfate flotation method, 600 patients with schistosomiasis had been examined by the Baroody and Most method and eggs of *S. japonicum* were found in 226 patients, but in no case was the diagnosis made by zinc sulfate. In 2 specimens, wrinkled masses of eggshells were found by zinc sulfate, but proper identification was impossible.

In reference to the brine flotation method, no patients with schistosomiasis japonica were discovered although the method was applied at least once in all patients.

So far as the acid ether method is concerned, there was an efficiency with this method of only 0.32 compared to water centrifugal sedimentation (1.00).

THE WATER centrifugal sedimentation method is simple and rapid, requiring no chemical reagents, and only a minimum amount of standard laboratory equipment. The method is to be recommended especially in treated cases, particularly when the other concentration methods have been tried and have proved unsuccessful.

Attention must also be called to the advances in the laboratory diagnosis of rickettsiosis caused by Rickettsiae or small bodies which have been proved to cause a number of very important diseases, not all of which are tropical. For instance, Rocky Mountain spotted fever has been found in many places in addition to Montana. Rickettsial diseases are those in which an animal reservoir or vector is important in the maintenance and transmission of the disease. Experimental behavior of this disease in laboratory animals constitutes one of the important means of diagnosis. We refer especially to the following rickettsial diseases: Q fever, classical typhus, murine typhus, and macular typhus in the Rocky Mountains, Colombia, Brazil, and Mexico, and also boutonneuse rickettsia, and the maculopapular rickettsia. In all of these, the use of animals is one of the important laboratory methods.

A number of serologic reactions are helpful in the diagnosis of rickettsial diseases, notably the use of the culture of Proteus X, namely, Proteus X_2, Proteus X_{19}, and Proteus XK, the last being a spontaneous variant of X_{19}. Complement fixation is important in diagnosis of many of the conditions.

The laboratory technic in the study of rickettsioses embraces (1) isolation of the virus in guinea pigs by injecting 10 cc. of venous blood from the patient; (2) the isolation of the virus in lice; (3) inoculation of fertile eggs; (4) the Weil-Felix reaction above noted, utilizing cultures of Proteus X_{12}, OX, and OXK; (5) the agglutination reaction of Weigl using a rickettsial antigen; (6) serum of Giraud, and (7) staining of the rickettsia using the Giemsa method.

For histologic section, the Wobeck method is used. The Castellanos method is also used in staining, as is the Macchiavello method. The Craigie method calls for the use of alkaline thiamine. Rickettsial cultures *in vitro* are very important in diagnosis and the complement fixation test reaction is used with the sheep hemolytic system, and antigen made from eggs.

Aseptic Necrosis of Bone
Management and Prognosis

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Bone undergoes aseptic necrosis as the immediate result of injury or occlusion of the blood vessels in the absence of infection. As in a case of infarction of the soft parts, the devascularized tissue dies within the course of a very few days. The idea that the bone may not die until months or years after the injury or vascular blockage is wholly fallacious and is the result of assumption that death occurs at the time when differences in density between necrotic and living portions become recognizable in roentgenograms, or when a dead articular portion breaks down from weight-bearing, both phenomena being late manifestations of aseptic necrosis.

The most frequent cause of aseptic necrosis from injury is fracture, but it may also be produced by dislocation, as of the hip, wrist, or ankle joint; by operation, as arthroplasty of the hip, or extensive stripping of fragments in the operative treatment of fractures.[1] A rare cause appears to be sprain or direct trauma to the nutrient vessels as in the case of the carpal lunatum.

Occlusion of the blood vessels of bone resulting in aseptic necrosis[2,3] may be produced by embolism, thrombosis, or localized obliterative vascular disease frequently of an obscure nature, but sometimes on an arteriosclerotic basis.

Fracture of the shaft of the long bones causes a certain amount of necrosis of the cortex of the ends of the fragments and of splinters, but bony union usually occurs in such cases in normal time since the callus is laid down by surviving periosteum and endosteum and the dead bone is subsequently replaced by new bone by a gradual process of creeping substitution. When the fracture involves the end of the bone and the shorter fragment is either entirely or mainly within the joint, its entire circulation may be cut off, leading to necrosis of the bone, marrow, and the articular cartilage. In such cases the callus can be laid down only by the end of the shaft fragment instead of by both fragments, and the incidence of nonunion is thereby appreciably increased.

Aseptic necrosis from fractures bordering on joints is seen most frequently in the head and neck of the femur, the carpal navicular bone, the lunatum, the astragalus, the capitellum of the humerus, and the head of the radius. Smaller necrotic lesions bordering on the articular surface of various joints may be separated by the trauma of usage and give rise to the picture of osteochondritis dissecans.

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Of these lesions, intra-articular fracture of the neck of the femur is by far of the greatest importance. The principal blood supply to the head of the femur comes by way of neck capsule branches of the anterior and posterior circumflex arteries, and when the neck is fractured near the head, all or most vessels may be severed regardless of the extent of the displacement of fragments. As a result, there is immediate cutting off of the blood supply to the major portion or all of the head of the femur. In some cases, the arteries coming by way of the round ligament are of sufficient size to maintain the circulation of the head, but more frequently they provide it with little blood supply, and if the neck is fractured the head becomes necrotic.

If the head becomes necrotic and nonunion follows[5, 6] the blood vessels grow in by way of the round ligament, of untorn portions of the capsule and of adhesions and slowly invade the dead bone, usually of the inferior portion of the head and in the vicinity of the fovea. They are accompanied by a fibrous callus which invades the cancellous spaces and in its deeper portions undergoes metaplasia and absorbs and replaces the dead bone and dead marrow by new bone and living marrow. The old dead bone, having no blood supply, cannot atrophy, and retains its original density as revealed by roentgenograms.

The living bone of the distal fragment gradually undergoes atrophy as a result of the marked disuse produced by the ununited fracture. Consequently it comes to cast a fainter shadow than the dead bone of the head or any newly formed bone in the head since the latter is spongy as a result of being deposited in an ununited nonfunctioning head.

This combination of atrophy in the distal fragment and of spongy bone in the transformed lower portion of the dead head makes it possible to recognize the necrotic portion of the head by the greater density of its shadow cast in roentgenograms. If the ununited fracture is left untreated, the dead bone may be slowly replaced by living bone so that within two or three years only a small amount of it remains, usually in the upper portion of the head. But the dead portion never collapses since, because of the nonunion, it is non-weight bearing. The articular cartilage, being deprived of its nutrition by tissue fluid derived from the blood supply of the underlying bone, undergoes extensive necrosis, and in the course of time is invaded by blood vessels and fibrous tissue, and very slowly replaced by a layer of fibrocartilage.

THE management of a necrotic head with nonunion depends on the duration of the fracture at the time when treatment is begun. If seen within the first one or two years while the head consists mainly of necrotic bone,[7] the fracture may be openly reduced through a Smith-Petersen incision, the fragments fixed by one or two rectangular tibial bone grafts inserted from the side of the shaft across the neck through the entire length of the upper portion of the head, and by threaded wires or screws similarly inserted from the side obliquely upward into other portions of the head.

The drilling of the upper portion of the head gets rid of a considerable amount of dead bone and opens the remaining portion for rapid invasion of the empty space alongside the rectangular grafts by callus and replacement by new bone. The grafts serve as struts to prevent collapse of the upper portion of the head and greatly increase the frequency of healing of the fracture of the neck. By this procedure the dead head may be transformed into living bone and the dead articular cartilage replaced by fibrocartilage with the preservation of the normal contour of the head and the reestablishment of a well-functioning hip. A tubular drill may be used for tunneling the head portion and the core saved as a biopsy for microscopic examination.

If the nonunion is of two or more years standing and the dead bone and dead articular cartilage have been extensively absorbed and replaced by frail new bone and fibrocartilage respectively, it is best to excise the head and perform either one of the various types of arthroplasty or an arthrodesis of the hip.

In case of a fresh fracture of the neck with death of the proximal fragment, bony union usually follows if the fragments are either impacted or well reduced and well fixed as by a Smith-Petersen nail or threaded pins. The callus and blood vessels grow from the distal fragment across the fracture line into the dead end of the neck and from there gradually invade the head, the dead bone being slowly replaced by new bone. At the fracture site the callus usually ossifies in the course of two to three months. If the patient is kept off the feet for a prolonged period up to as much as two or three years, the dead bone may all be replaced by new bone without collapse of the weight-bearing portion of the head from pressure against the acetabulum, and a well-functioning hip is re-established.[8] However, if weight-bearing is permitted, the portion of the head underlying the acetabulum will be broken off when, many months after the fracture, the invading new bone reaches its margin because the zone of replacing new bone is temporarily soft and too weak to stand the pressure. The collapse of the remaining dead portion leads to deformity and degenerative arthritis and a poor functional result.

The broken-off dead portion may eventually become reattached and replaced by new bone, or occasionaly it remains practically unchanged with an ununited fracture line separating it from the underlying bed similar to the loose body from the femoral condyle in osteochondritis dissecans at the knee. In a certain percentage of cases of fracture of the neck with aseptic necrosis in which pin or nail fixation is employed, the fracture fails to unite and the neck is slowly eroded and shortened. In other cases, the fracture unites but months later a re-fracture occurs a short distance proximal to the old fracture line as weight is thrown upon the weak invading zone of new bone.

The roentgenographic recognition of a dead head produced by fracture of the neck is much more difficult if the fracture unites than if it remains ununited.[7] This is because when the fracture unites and the limb is used, there is little or no atrophy of disuse of the distal living fragment and its density remains almost the same as that of the dead head which cannot atrophy. On the other hand, in case of nonunion there is little use of the extremity and marked atrophy of disuse of the distal living fragment which in consequence casts a much fainter shadow than that of the dead head.

Aseptic necrosis of bone produced by lesions other than tearing the blood vessels in injuries is relatively common in certain epiphyses and short bones during childhood and adult life. Familiar examples are Legg Perthes' disease of the hip, Osgood-Schlatter's disease of the tibial tubercle, Köhler's disease of the tarsal navicular and the metatarsal bones, and Calvé's disease of the vertebral bodies. These lesions form a special group and will not be further considered here.

NONTRAUMATIC aseptic necrosis is less frequent in adults than in children and presents a somewhat different clinical picture. The etiology in the majority of the cases is obscure. Best known cause is caisson disease[3] in which the excess nitrogen taken up by the blood and tissue fluids during the period spent by the worker in compressed air is liberated as a gas when decompression is too rapidly effected.

The exact method in which the gas acts upon the bones is imperfectly understood. It may be through arterial embolism or through direct pressure on the bone marrow which is rich in fat and absorbs the nitrogen in large quantities. The lesions are located in the long bones of the extremities and may affect either epiphysis or diaphysis, and not infrequently both epiphysis and diaphysis of one or several bones. The most frequent sites are the head and neck of the femur, the head of the humerus, the lower end of the femur, the upper and lower ends of the tibia, and the upper end of the shaft of the humerus. The bones of the trunk and the short bones of the extremities are practically never involved.

Large infarcts bordering on the articular cartilage are common in the head of the femur and humerus and are frequently bilateral.

Large to small infarcts are found less frequently in the shafts of humerus, femur, and tibia, and rarely in the fibula. The infarcts of the shaft are gradually invaded about the periphery by blood vessels and fibrous tissue with properties similar to callus. They occupy the cancellous spaces and absorb the dead marrow and cancellous trabeculae, replacing them by living trabeculae and living marrow.

This creeping replacement of the dead bone by new bone may go on over periods from months to two or three years, and it may involve inner portions of cortex which has lost its circulation. Small infarcts may be completely replaced. But with large infarcts when the replacement process has advanced to the point at which the new bone is strong, the reparative stimulus may be exhausted. Large to small areas of dead bone may be left permanently, and calcification of the fibrous zone of invasion about the periphery and of scant small islands of the interior may come about much as in the case of old infarcts of the spleen or kidney. Infarcts of the diaphyses produce little or no symptoms and are not recognizable in roentgenograms until years after formation when the calcification casts heavy shadows in roentgenograms that are characteristic of the lesion.

Aseptic necrosis of the head of the femur usually involves the entire structure including bone and its overlying cartilage, although in some instances small portions of the lower part of the head appear to remain alive. Following the occurrence of embolism, there is gradual invasion of the dead bone of the head by blood vessels and callus-like tissue coming from the neck and sometimes from the round ligament with replacement of the dead bone and dead marrow by living bone and living marrow similar to that which is described for infarcts of the shaft.

Single or, more frequently, multiple infarction of epiphyses and diaphyses similar to that produced by caisson disease may be produced by vascular occlusion from other causes, most of which are very obscure.[4] In some cases the lesions develop in elderly individuals affected by cardiovascular disease, and obliterative arteriosclerosis may be the direct cause of the infarction. There is little evidence that multiple arterial embolism has been the exciting cause in the few cases that have come to autopsy, since embolic infarction of the soft tissues which might be expected as an accompaniment has not been found. Rheumatic fever and rheumatic heart disease may have been the exciting cause in one case studied. Single or multiple infarction has been accompanied by degenerative arthritis in joints remote from the lesions with sufficient frequency to suggest an etiologic relationship between the two conditions. Further studies will be necessary before the causes of multiple nontraumatic aseptic bone infarction are understood.

The clinical course and management of necrosis of the head of the femur are much the same whether in fractures of the neck of the femur followed by bony union, dislocations of the hip, or nontraumatic lesions such as caisson disease and obscure obstructive arterial disease. The callus-like fibrous tissue which grows from the neck into the dead head slowly absorbs and replaces the dead bone by new bone. During the initial stages of invasion and replacement, the changes proceed asymptomatically and there is little interference with function of the hip. The head of the bone retains its contour and density and the condition can usually not be recognized in roentgenograms.

After several months to a year or two the invasion in all of these conditions reaches the weight-bearing part of the head from the lateral and inferior portions, and as the stress from the acetabulum is thrown upon the zone of replacing new bone, it fractures because it is at first weaker than the old dead bone which it has replaced.[5] The broken off portion of dead bone lying beneath the acetabulum then begins to collapse from further weight bearing. If roentgenograms are taken as soon as the hip becomes painful, the occurrence of the fracture may be recognized early while there is extremely little displacement, and the opportune time

for treatment is then at hand. If further weight bearing is permitted, the broken off dead bone will be downwardly displaced, the head gradually deformed, and degenerative arthritis set up.

Patients with beginning collapse of the head have been placed on crutches and forbidden weight bearing over long periods up to two or three years, but despite this drastic therapy the head usually flattens to some extent and deforming arthritis is established, leaving a poorly functioning hip. The ideal treatment in this early stage of recognition should aim at the prevention of further collapse of the head and rapid replacement of the dead bone by new bone and of the dead articular cartilage by fibrocartilage.

Recently in a limited number of cases, an operation has been employed similar to that described for ununited fracture of the neck with death of the head which has yielded results superior to those obtained by most of the methods in common practice. The lateral surface of the shaft is exposed through a 6-inch incision extending downward from the greater trochanter. With x-ray control, a 1 cm. drill hole is made extending obliquely upward and inward through the upper portion of the neck and head, perforating the overlying articular cartilage. A second drill hole is started about 2½ cm. below the first and directed slightly more obliquely upward so that it perforates the articular cortex and cartilage approximately 1 cm. below the first drill hole. If a Smith-Petersen nail has been used and the fracture has united but the head has later collapsed, the nail is removed and the second drill hole is made through its channel. Two bone grafts, each 1 cm. broad and the length of the tunnel, are taken from the anteromesial surface of the tibia and inserted sagitally into the tunnels ending just short of the articular surface.

The wound is closed and the patient is kept on crutches for nine months to a year depending on the clinical course and the appearance shown in roentgenograms. The drill removes a considerable portion of the dead bone. The grafts act as strong struts to prevent collapse of the upper portion of the head during the period of invasion and replacement by new bone. There is room between the walls of the round holes and the rectangular pegs for the ingrowth of blood vessels and callus from the neck side into the remaining dead bone of the head. This brings about a relatively rapid invasion and transformation of what is left of the dead head, and fibrous tissue grows out of the proximal end of the hole onto the articular surface, invading, absorbing, and replacing the dead articular cartilage by fibrocartilage.

Thus a head of normal strength and contour, covered by living cartilage, is relatively rapidly created, and degenerative changes in the hip joint are reduced to a minimum. Patients treated this way have an excellent clinical result characterized by freedom from pain with almost a normal range of motion and good weight bearing after one year.

If the patient is not seen until late when the head of the femur is markedly broken down and the joint is badly crippled, an operation may be indicated, such as a vitallium cup or other arthroplasty or arthrodesis of the hip joint.

Necrosis of the proximal and/or rarely the distal fragment of the carpal navicular results from fracture of that bone in a considerable percentage of the cases. It predisposes to nonunion and may be diagnosed after the lapse of a few weeks by the presence of greater density in the dead fragment than in the atrophied living fragment and the surrounding wrist bones. Early treatment by an intramedullary bone peg leads to bony union and replacement of the dead bone by living bone with less tendency to the establishment of degenerative arthritis in the carpus than is seen in the old neglected cases or in long-standing necrosis of the navicular bone.[9]

When the neck of the astragalus is broken, the blood supply of the body of the bone may be interrupted, causing death of the fragment. In exceptional cases the distal fragment may also become necrotic which predisposes to nonunion.[1] Necrosis usually leads to more or less

breaking down of the body fragments and degenerative arthritis which may be so severe that arthrodesis of the ankle may be called for. Similar changes including loose bodies may result from aseptic necrosis following intra-articular fracture at other joints of the body, and plastic or arthrodesing operations may be necessary to relieve pain and improve function.

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Treatment of Alcohol Addiction

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THERE are about three million excessive, uncontrolled drinkers in this country. Of these, about 600,000 are suffering from bodily or mental, or both bodily and mental diseases resulting from excessive use of alcohol. These are the well-known diseases of chronic alcoholism. I do not think it is necessary to discuss the therapeutic procedures employed in treatment of diseases following excessive drinking over a long period of time, since these diseases are mostly due to vitamin deficiencies and their treatment is based on the awareness of their nutritional origin.

It is more important to focus attention on addiction to alcohol itself. At Yale University, work on problems of alcohol addiction had been going on for many years. In 1944 it was decided that something should be done in the line of active treatment of addiction to alcohol. In March 1944, two free clinics for the treatment of addictive drinkers were established in Connecticut, one in New Haven and the other in Hartford, as an experimental project of the Laboratory of Applied Physiology of Yale University, in order to test the possibilities of large-scale rehabilitation of alcoholics at a limited cost.

Last year, as a result of legislation enacted by the State of Connecticut, the Hartford Clinic was turned over to the state. The New Haven Clinic, however, will remain under the supervision of Yale University.

I shall try to describe as briefly as possible our therapeutic procedures at the New Haven Clinic. Our staff is made up of a consultant in psychiatry, an internist with a background of psychiatric study, two social workers, a psychologist who devotes only part time to the clinic (mainly to psychologic testing), and one educator, who, because of his training, seemed particularly fit to deal with problems relating to alcohol addiction.

There were objections to the setting up of a specialized clinic for alcoholics. However, there are many indications for clinics of this type. We know, of course, that addiction to alcohol is the result of many causes. We do not know of any physiologic deviation underlying all cases of addiction. We know mainly of precipitating factors. There is no doubt that a number of addictive drinkers were treated in the past and are still treated in nonspecialized clinics, both medical and psychiatric. However,

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it appeared justifiable to set up specialized clinics because we felt that when true addiction to alcohol is present, irrespective of the causative factors involved, there are similarities among alcoholics which justify singling them out of other groups of patients. It is sufficient to mention these similarities: Because of their socially unacceptable behavior they are more or less constantly at odds with their environment; intoxication is constantly the most obvious symptom they offer; alcohol itself represents for them the most cherished source of pleasure and at the same time the most appealing means of wiping out pain.

Because treatment at the clinic is carried out on an ambulatory basis, we have some limitations. We have to exclude patients who are severely intoxicated. We refer these cases to hospitals or to private institutions. We have to exclude all psychotic patients whose place is either in state hospitals or in private institutions. Patients who are temporarily suffering from medical diseases either due or not due to alcohol, and who require hospitalization, are also excluded.

There still remains a large number of addictive drinkers who can be adequately treated on an ambulatory basis. We feel that ambulatory treatment is preferable whenever possible, because many times hospitalization or confinement in an institution represents for the addictive drinker another way of escaping a difficult situation.

We take care of patients just out of a bout, patients in that stage which is usually labeled "hangover." Hangover is that period which begins when the concentration of alcohol in the blood falls to relatively low levels and the patient is again aware of a painful reality, and ends when the patient is back to a situation which is similar to or slightly worse than it was immediately preceding the last bout.

We feel that immediate interruption of drinking is required at this period. The patient in hangover is usually overflooded with pain, both physical and mental. Unless help is given at this stage of the addictive process, he is apt to resort again to alcohol in order to wipe out both the physical and the mental pain. Sedation is required in most cases at this stage, but we feel that it is not sufficient. It must be immediately complemented by psychotherapy, which should begin as soon as possible.

Close observation of the patient in the hangover stage is most helpful in reaching some diagnostic impression of the main problems underlying his addiction. During this stage there is a magnification of both bodily and mental symptoms which appear more obvious than they do during intermediate periods of sobriety. Also, the patient is less aggressive than usual and is more receptive to therapeutic approaches.

When the patient comes to the clinic in a period of temporary sobriety in order to achieve permanent sobriety, our approach is more or less as follows: We try to evaluate as rapidly as possible the main problems underlying the individual's uncontrolled drinking. Usually the addictive drinker faces very serious difficulties in his environment, difficulties which must be realized and evaluated at once.

The patient is given a physical examination to determine his physical condition and the possible presence of physiologic deviations. A psychologic study follows and is complemented, if necessary, by psychologic testing.

Therapy begins immediately, proceeding in some way from the periphery to the core. Our first attempts aim at the correction of environmental difficulties. Family disharmony is present in a great number of cases; so are employment problems and conflicts with the law. We often need the cooperation of other social agencies interested in this problem. It is evident to us that the greater these difficulties are, the worse the prognosis in the case. As a matter of fact, the cases that have had a long history of conflicts with the law are of very doubtful prognosis.

Following this attempt at correcting the environmental factors and sometimes parallel to it, we try to remedy all bodily disorders, whether due to alcohol or other causes. We pay

specific attention to disorders which are most often observed in individuals addicted to alcohol. An example of this is hypoglycemic fatigue, which sometimes can be corrected, at least temporarily, with proper medication. We note also the possible presence of disorders of the glands of inner secretion. Disorders of this kind are especially frequent in alcoholic women. A large group of women start drinking at menopause; their addiction can often be favorably affected by proper hormonal treatment.

The treatment of addiction itself is mainly a psychologic one. Medication can be used, but is usually only an adjuvant. Mention should be made of amphetamine sulfate, a drug which might relieve the patient of the frequent feeling of fatigue and which often gives him a sense of well-being and makes him more receptive to psychotherapy.

A strictly medical approach to the problem of alcohol addiction is the so-called conditioned reflex treatment or aversion treatment, an attempt to create an aversion to alcohol by means of injections of emetic drugs. We believe that this approach has its definite place in the treatment of alcohol addiction. However, we feel that it is doomed to failure unless complemented by psychologic approaches as soon as possible.

The psychologic approaches to the problem are many, but are all, however, based on the following assumptions: First, it is impossible to shift from an uncontrolled pattern of drinking to a controlled one. The few, not completely proved exceptions to this rule do not challenge its validity. Therefore, the aim is permanent sobriety. Second, permanent sobriety can be achieved only if corrective emotional experiences occur in the personality of the patient. There is no doubt that in many cases these corrective emotional experiences can be elicited only by a rational use of strictly psychiatric technics. We have found that a combination of individual therapy with group therapy is most helpful in many cases.

Psychotherapy, though always under psychiatric supervision, is carried out in our clinic also by the social worker, the internist, and the educator. The educator supervises the program of group therapy.

Alcoholics can also be helped by approaches other than psychiatric ones. An outstanding example of a nonpsychiatric approach to alcohol addiction is embodied in the program of Alcoholics Anonymous, an association of formerly uncontrolled drinkers who, in helping other drinkers to achieve sobriety, help themselves to keep sober. A rational analysis of the psychologic mechanisms underlying the successes of Alcoholics Anonymous shows that they employ, though on a more intuitive basis, some of those psychologic tools which are used in orthodox psychiatry, such as emotional support, persuasion, catharsis, insight, etc.

There is no doubt that other approaches, such as religion, can be helpful in some cases. It is our aim to take care by psychologic or medical means, of all those patients who cannot be handled otherwise, and to pave the way for contacts with other organizations for all those patients who can be helped outside our institution.

We feel that the program of rehabilitation of alcoholics is a very long-term proposition which requires years in many cases.

As far as our results are concerned, we see about 30 new patients each month. The clinic is completely free and patients belong to every walk of life. About 50 per cent who contact us drop out of the picture after two or three interviews. Of the remaining 50 per cent, about half achieve permanent sobriety after a period of three, four, and sometimes six months. The other half keep on drinking. However, we feel that even in these cases the clinic has had a marked impact on them. It appears that more often than not the drinking episodes are spaced and sometimes shortened, that there is a better adjustment of the addictive drinker to his family, to his job, and more important than anything else, to himself.

DIAGNOSTIC CLINIC

Middle Lobe Syndrome

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MIDDLE LOBE atelectasis of nontuberculous origin with suppurative changes has within very recent years been encountered with unprecedented frequency. Puzzled at first by how often the middle lobe was involved, we were struck by the logic of Brock's[1] explanation of middle lobe atelectasis in tuberculosis. This observer pointed out the strategic location of the middle lobe bronchus in relation to lobar lymph nodes (Figure 1) and showed how bronchocompression from these nodes was the causative factor in the so-called bronchostenosis and nonaeration of the middle lobe in tuberculosis. As he has re-emphasized in his splendid study of the tracheobronchial tree,[2] the middle lobe bronchus lies at the apex of the lymphatic pathways from both upper and lower lobes. It is then particularly vulnerable from the standpoint of lymphadenopathy impingement (Figure 1).

More recently Zdansky[3] quite independently has been impressed by the vulnerability of the middle lobe bronchus to lymph node enlargement and has termed the middle lobe bronchus a "punctum minoris resistentiae." He has demonstrated at operation middle lobe atelectasis secondary to bronchial compression by enlarged lymph nodes in nontuberculous cases.

To date we have been able to study twelve examples of bronchial compression of the middle lobe bronchus by enlarged lymph nodes in nontuberculous cases. In general, the picture clinically has been fairly consistent. Hemoptysis and recurrent episodes of pulmonary infection have been the major presenting symptoms. Only two patients in this group failed to manifest one or both of these features as their chief complaint (Table 1). Sputum, which is generally characteristic of bronchiectasis, varies in amount. Chronic cough, of course, is universally present in these patients. The onset in some cases is marked by a severe acute febrile episode usually diagnosed as pneumonia or "flu." In others, the onset is more insidious. In the intervals between episodes, the patients as a rule are not well. They complain of easy fatigability and are unable to carry on their usual work.

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CASE HISTORY

I. M., 31-year-old white female, was admitted to the Barnes Hospital in 1947. She stated that her illness began six years previously with a

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moderately severe respiratory infection of unknown etiology. This episode was associated with fever of approximately one week's duration. Following this she had persistent cough productive of a small amount of sputum until 1943 at which time she had another acute episode characterized by fever and prostration. After the subsidence of this episode, cough with moderate amounts of sputum continued. A third acute flare-up similar to the previous two was experienced in 1945. Productive cough continued. Occasionally the patient would expectorate blood-streaked sputum.

Physical examination revealed signs of atelectasis over the area of the middle lobe of the right lung. Laboratory findings were essentially negative. X-ray films showed a typical picture of atelectasis of the middle lobe. Lipiodol bronchograms demonstrated a block of the middle lobe bronchus, and bronchoscopy showed it to be obstructed to such a degree that not even a small suction tip could be forced into its lumen. A biopsy of the mucosa of this area showed only chronic inflammation.

TABLE 1
PRESENTING COMPLAINTS

SYMPTOM	NUMBER OF CASES
Hemoptysis	7
Recurrent pneumonitis	3
Chronic cough with sputum	2

At operation a small totally atelectatic middle lobe was found, the bronchus of which seemed to be compressed by a large firm lymph gland lying on the inferior surface of the bronchus near its beginning. The removal of the lobe was followed by an uncomplicated postoperative convalescence. She has remained well for a period of sixteen months since operation.

X-ray findings—The x-ray findings were uniformly those of atelectasis of the involved lobe (Figures 2 and 5). Occasionally these shadows had been mistinterpreted as being due to interlobar effusions. Lipiodol studies were not done routinely, but when done revealed either nonfilling of the involved bronchus or a contracted bronchiectatic pattern.

Bronchoscopy—Bronchoscopic findings revealed marked cicatricial stenosis of the middle lobe bronchus in every case. Usually the orifice was slit-like. In any event the lumen distal to the origin of the middle lobe bronchus invariably gave evidence of definite obstruction. Depending upon the time interval from the last episode of superimposed infection, there was a greater or less degree of nonulcerative inflam-

matory edema and congestion about the orifice. No broncholiths or foreign bodies were found in any case. In the majority of cases, pus was found coming from the middle lobe orifice. The remainder of the tracheobronchial tree showed no signifiant changes.

Operative findings—At operation there was in all cases a small totally atelectatic middle lobe (Figure 3). Universally, the proximal portion of the middle lobe bronchus was compressed by enlarged, firm lymph nodes. The key node from the point of view of compression was most frequently found on the inferior surface of the bronchus. The compression was definite and unmistakable, and when the node was removed, the groove in the bronchus remained.

Pathology—Pathologically, the lobes were atelectatic, with varying degrees of interstitial fibrotic change. The bronchi were dilated and presented the characteristic changes of bronchiectasis. There was pseudostratification of the mucosa with loss of cilia. Areas of metaplasia, submucosal loss of elastic tissue, and fibrous tissue replacement of cartilage were common findings. In some cases multiple small abscesses were present in the lobe (Figure 4).

The main bronchus to the middle lobe showed cicatricial stenosis most prominent at the point of maximum compression. This point was easily correlated, since as pointed out, the enlarged node or nodes invariably left an indentation plainly visible on the external surface of the bronchus.

The lymph nodes were not remarkable except for size and consistency. In each case the nodes were markedly enlarged and firm. Histologic section showed only the changes of a chronic, nonspecific lymphadenitis.

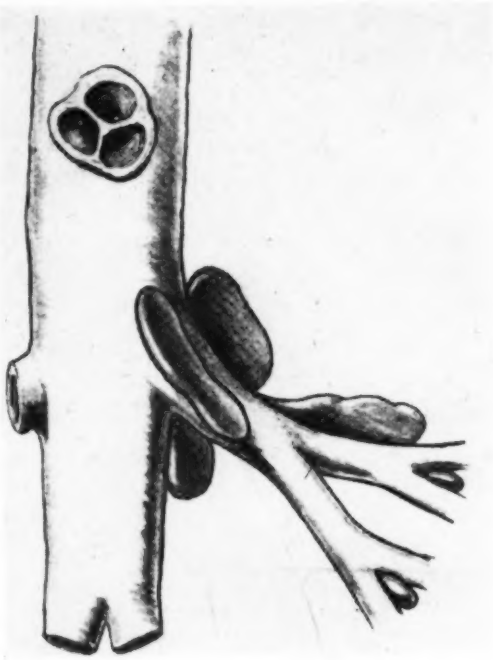

Figure 1. Diagram of middle lobe bronchus showing lymph node arrangement. Reproduced from Brock, R. C.: *The Anatomy of the Bronchial Tree*. Oxford Medical Publications, 1946. *(By permission of the author and publisher.)*

DISCUSSION

In trying to find a satisfactory explanation for the present frequency of this previously unnoted syndrome, we considered first the influence of the sulfonamides and the antibiotics. It seemed reasonable that these agents, particularly penicillin, with its known efficacy in pulmonary infections, and its almost universal exhibition by physicians whenever pulmonary inflammation exists or is suspected, might be responsible. Infections of the lung which in pre-penicillin years went on to fatal pneumonias or which suppurated to give frank lung abscesses might well now be so attenuated that a less fulminating picture supervened. The previously mentioned contribution of Brock which so admirably explains the bronchial obstruction very nicely completed the picture. Unfortunately, when a sufficiently large series had been accumulated, a careful scrutiny of the case records failed to demonstrate any relationship between the lesion and penicillin, nor indeed was any etiologic common denominator apparent.

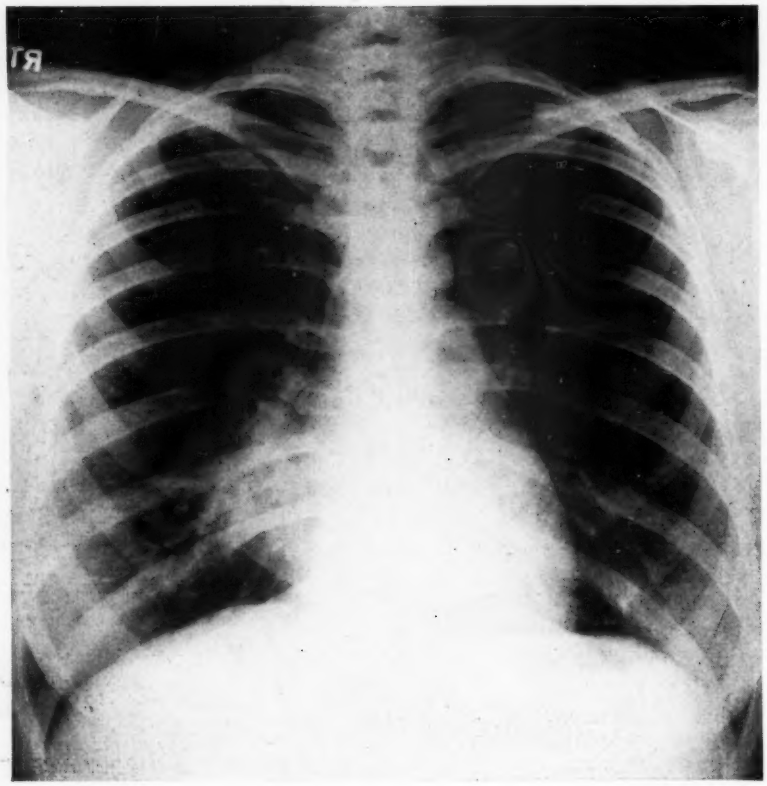

Figure 2. X-ray of typical middle lobe atelectasis showing PA view.

In this group of twelve cases there were only three to whom penicillin had been administered at the time of the initial episode. In five of the cases penicillin had never been given prior to coming under our observation. It is thus impossible to make out a case for penicillin attenuation of otherwise lethal or frankly suppurative infections.

That the atypical or virus pneumonias might be responsible also lacks any real confirmation. While this disease not infrequently results in delayed clearing of areas of lung as demonstrated by physical findings, and x-ray, these areas of residual infiltration are patchy and an exhaustive review of the literature has failed to reveal evidence that the persistent areas last longer than several weeks. Moreover, the patient with a residual opacity following virus pneumonia is clinically well and never manifests the signs and symptoms secondary to bronchial obstruction. To our knowledge, no one has reported persistent middle lobe atelectasis following atypical virus pneumonia.

A very critical examination of the pathology as well as the clinical histories of the patients reported in this series fails to give a clue as to why this lesion had not generally been seen more frequently in the past. It is altogether likely that no single factor is responsible but that any inflammatory process which leads to lobar hilar lymphadenopathy may be followed by bronchocompression, bronchostenosis, and middle lobe atelectasis. Certainly once the lymphadenopathy has developed, the essential

Figure 3. View at operation showing atelectatic middle lobe.

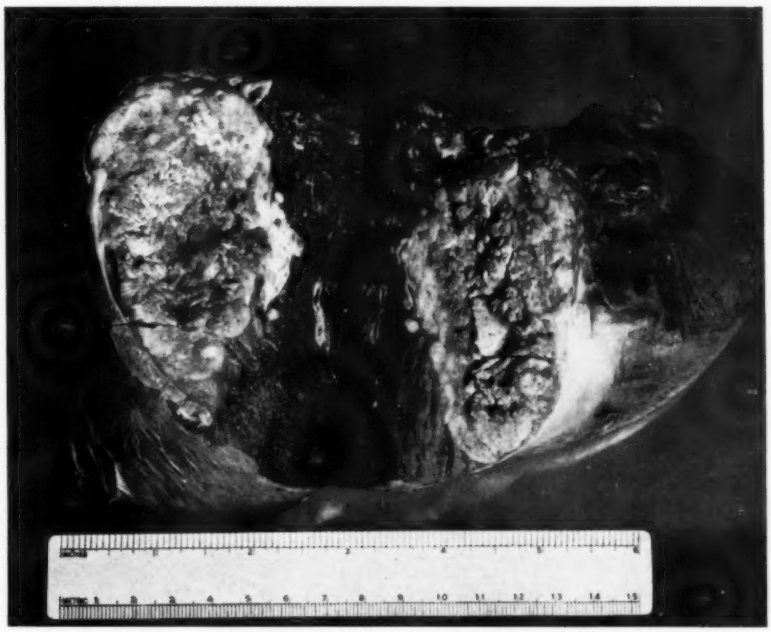

Figure 4. Resected middle lobe showing lung abscess secondary to obstruction.

Figure 5. Lateral x-ray view of middle lobe atelectasis.

step in a vicious circle has become established. Obstruction to the bronchus inevitably leads to infection and the infection perpetuates the lymphadenitis.

The impression is not to be left that the stenosis results purely from the pressure of lymph nodes. The bronchial stenosis may not be due entirely to pressure by enlarged glands but may in part be caused by spread of infection through the bronchial wall from the glands with resultant edema and even, at times, stricture.

It is pertinent to emphasize that in the investigation of these cases all lobes should be investigated since it is possible for the original primary lesion to have been located in the lower or upper lobe on the right side and the middle lobe to have become involved more or less as an innocent bystander because of its strategic position.

The treatment, of course, is obvious and has been simple. In all twelve cases a middle lobe lobectomy by the individual ligation technic was carried out. All patients made perfectly uneventful recoveries and have remained free of symptoms since operation.

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DIAGNOSTIC CLINIC

Treatment of Diseases of the Thyroid

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In this clinic I should like to emphasize the rationale of the treatment of hyperthyroidism, whether this treatment be medical or surgical, and point out some of the indications for thyroidectomy in the treatment of various types of goiter. As a case study we have a patient who illustrates some of the fundamental signs and symptoms observed in early hyperthyroidism.

The patient is 44 years of age. Her symptoms are of particular interest as she did not know that she was sick at all. She entered the hospital because of a completely different complaint, and, during the course of routine examination, objective signs of early hyperthyroidism were observed. She was found to have a small diffuse goiter. She was nervous, although she had hardly paid any attention to it herself, and it was noted that she had a persistent tachycardia while at rest.

It is significant that this patient did not realize that she was sick, yet she had hyperthyroidism. A sensation of illness is not characteristic of early hyperthyroidism. I think one must beware of patients who complain of fatigue, of prostration, of nervous exhaustion, and who have symptoms suggestive of hyperthyroidism without the signs. Hyperthyroidism, after all, is an organic disease; it is a disease in which the entire metabolic system of the body is deranged. Hypermetabolism is characteristic of this disease, and hypermetabolism expresses itself in a stimulation of the circulatory system and by other manifestations which are objectively evident, as with the patient now under discussion.

The goiter here is not large. It is barely palpable. It is important, I believe, in examining the thyroid always to have the patient stand, always to have the head erect, not hyperextended—a position which tenses the muscles—not bent so that the gland dips below the clavicles, but with the head in a natural position. Then the thyroid is readily palpable on deglutition.

The patient also has a fine tremor, which is hardly visible but is easily palpable. You can often feel the tremor better than you can see it. The hands are moist and warm, and there is a persistent tachycardia and a forceful apical impulse—again an expression of the attempt of the circulatory system to compensate for the hypermetabolism.

Here we have objective evidence of early hyperthyroidism, so early that the patient was not aware of it, so early that the thyroid itself is barely palpable.

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Now the problem of treatment of this condition comes up. Here is a patient who is not aware of illness. She would not willingly rush to the surgeon to have the thyroid removed at this time. This, in my opinion (and I am sure in her opinion), is an ideal case for the medical treatment of hyperthyroidism. If this medical treatment is carried out properly, fully, and over a long enough period of time, there are good prospects that this patient may obtain a long-standing, if not a permanent, remission by medical means alone and that surgery will not be necessary.

I DO NOT believe it would be fair to the patient to tell her that surgery is necessary or will eventually be necessary and prepare her either with iodine or with an antithyroid drug and perform a thyroidectomy. If this patient is prepared with an antithyroid drug and her metabolism reduced to normal, it would be better to continue the treatment for a little longer and see if she will not spontaneously enter a long-standing or permanent remission.

Also, it is not fair in such a patient to state that surgery will not be necessary. She has just been started on propyl thiouracil. We do not yet know how her hyperthyroidism is going to react to this drug. It is entirely possible that the gland may enlarge rapidly under treatment, as is sometimes the case, and under such circumstances thyroidectomy does become necessary. Therefore, the best way to handle this particular problem is to say, "You have a disease which appears at the present time to be well adapted to medical treatment. We cannot promise you that surgery is not eventually going to be necessary, but we believe that medical treatment is worth a trial in that it will give you probably better than a 50-50 chance of entering a long-standing if not a permanent remission."

What are we going to attempt to do? What is the rationale of the medical treatment, or of surgical treatment for that matter? We know too well from our experience with iodine that it does not commonly cure hyperthyroidism. Iodine alleviates the symptoms temporarily.

We know that if we give iodine to a patient with a +75 basal metabolism who has not had iodine before, the metabolism usually will fall to a little less than half the previous level. Between 25 and 50 the metabolism will form a plateau. We also know that iodine, no matter how long it is given nor in what doses, will rarely drive the metabolic rate to lower levels. There is a persistent residual hyperthyroidism present in these cases; as long as that residual hyperthyroidism is present, the hyperthyroidism becomes worse on withdrawal of iodine. The patient is again in as severe a state as she was in the beginning.

What happens with thyroidectomy? In the early days of thyroidectomy the operation was often incomplete; not enough gland was removed, and the metabolism would fall perhaps to +10, perhaps to +15 per cent, and stay at that level. The patient was gratified. She felt much better, she gained weight, and symptoms were relieved. However, critical examination and, most important of all, accurate determina-

tion of the basal metabolic rate indicated that a residual hyperthyroidism was present. In the presence of a low-grade postoperative residual hyperthyroidism, cures of hyperthyroidism were rarely seen. These are the patients in whom the hyperthyroidism recurs, usually within a year of operation.

Why do not all patients have a recurrence of their hyperthyroidism after thyroidectomy? That is a thing we do not understand, because the mechanism that produced the original hypertrophy and hyperplasia of the thyroid is still present after subtotal removal of the thyroid gland. Inasmuch as that mechanism is still present, why does it not induce the remnants of the thyroid again to undergo hypertrophy and hyperplasia and again to produce hyperthyroidism in that individual? The only answer which we have is speculation that an adequate thyroidectomy in which the metabolic rate is driven to subnormal levels, to —10, —15 per cent, and maintained there for a period of time, breaks some vicious circle in the course of the disease. The hyperthyroidism then goes into a remission just as it occasionally goes into a spontaneous remission without any form of therapy. An adequate thyroidectomy, then, will cure the disease. Inadequate thyroidectomy or iodine therapy will not cure the disease.

I make this analogy because it is so important for one to realize it when using the antithyroid drugs. Propyl thiouracil, particularly, is a weak antithyroid drug as compared with the parent drug, thiouracil, and only produces an iodine block, as Dr. Astwood has found, that is to say, a block in the uptake of radioactive iodine for four hours after an adequate dose, whereas thiouracil produces a block for twenty-four hours.

In other words, the block in formation of thyroid hormone after an effective dose of propyl thiouracil is a short block, and that is why some patients are found to be resistant to this drug. In some patients, in spite of adequate dosage, the metabolism falls to only +10 or +15 per cent. So in those patients whose metabolism is not completely controlled by propyl thiouracil, regardless of how long one continues the treatment, there is still some residual hyperthyroidism, and the situation is exactly comparable to that of the patients who were treated with iodine and that of the patients who had an inadequate thyroidectomy with a low-grade residual hyperthyroidism.

Recurrences will be the rule in those patients inadequately treated with propyl thiouracil. It may be that propyl thiouracil will not be the ultimate answer for all patients; it may be that methyl thiouracil or some other derivative of thiouracil will be more effective in the long run in causing a universal and complete control, driving the metabolism to zero or even to subnormal levels.

In the meantime, however, the majority of patients do respond in a satisfactory manner to treatment with propyl thiouracil. Most of them can reach zero or less if adequate doses of 300 mg. daily are given. It should be remembered, however, that the dose should be distributed as widely as possible through the day because of the short action of the block in this drug. It should be given at least four times daily, after every meal, and at bed time. It should not be given in just morning and night dosages, for then the thyroid will make a complete recovery from the block before the next dose is given.

In the treatment with antithyroid drugs we are aiming, not merely to relieve the patient's symptoms, or to reduce the metabolism to the upper limits of normal, but to control the disease completely; we are aiming to block the vicious circle which we presume causes this disease and to accomplish exactly the same thing as an anatomic thyroidectomy does, namely, a physiologic thyroidectomy, bringing the patient to a normal thyroid or a hypothyroid state. If we fail to accomplish this our chances of accomplishing cure by medical means are reduced to insignificance.

I think it is safe to say, therefore, that at the present time the responsibility for the treatment of hyperthyroidism has shifted. It used to be the responsibility of the surgeon to perform an adequate thyroidectomy and to prevent re-

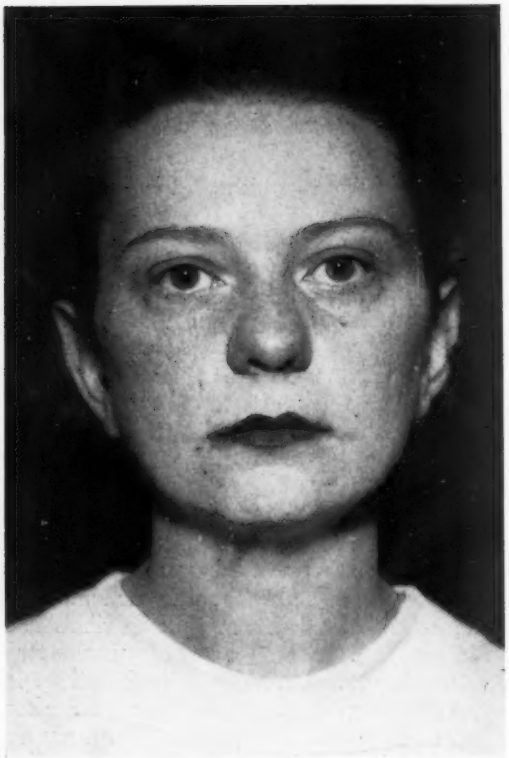

Figure 1. Small diffuse goiter with hyperthyroidism suitable for definitive treatment with propyl thiouracil.

currences of hyperthyroidism. Today the challenge is with the internist. The internist is challenged not only to reduce the metabolism to zero or less, but he must maintain it at that level over a long period—sometimes a year. The exact length of time needed to produce a long-standing or permanent remission is not known.

It may be that more intense treatment carried out over a shorter period of time will be as effective as maintaining a normal thyroid activity or slightly hypothyroid state for a longer period of time. We know that the metabolism must be driven down and must be maintained at those levels if a long-standing remission is to be accomplished. We also know that if this is done, the incidence of long-standing remissions will be at least 50 per cent—I believe much closer to 75 per cent—in those patients who can be carried through this length of time.

A CERTAIN percentage of patients are resistant to treatment with propyl thiouracil. That is why when one first sees a patient one cannot state, "We can cure you medically," because one does not know what the reaction to the drug is going to be. Some patients will respond slowly, some will respond incompletely; in some of them, extremely high doses will be required, and the resistant patients will usually be the ones who will develop recurrences as soon as the drug is withdrawn. Finally, the gland may enlarge under treatment. This is a bad sign. In those patients whose glands enlarge, the recurrences usually take place promptly and one has to discontinue the medication because of the progressive enlargement.

Therefore, in those patients who do not respond satisfactorily to an empiric trial (and they constitute at least 25 per cent of the patients with Graves' disease) the internist should not force the issue; he should not attempt, regardless of the type of response, to make the patient go on with medical treatment when it becomes clear that surgery would give a more prompt and definitive answer to the problem.

At the present time, therefore, our plan of treatment is as follows. The patients are divided roughly into four groups:

(1) Those patients with Graves' disease with goiters of moderate size. If the gland is of small or moderate size, which is the case in 85 per cent of the patients with Graves' disease, then I think it is worth a trial at medical treatment, provided one can have the full cooperation of an intelligent patient who will do exactly as one says over as long a period as recommended. However, if the goiter is large enough to be visibly deforming, that is to say, a big diffuse goiter, I believe it is foolish to try to treat it indefinitely by medical means. These often enlarge further under treatment and it is better to advise preparation with an antithyroid drug and thyroidectomy (Figure 1).

(2) Those with large goiters, either adenomatous or diffuse. These patients can be pre-

Figure 2. Large diffuse goiter with hyperthyroidism suitable for preparation with propyl thiouracil and thyroidectomy.

Figure 3. Nodular goiter with severe hyperthyroidism suitable for preparation with propyl thiouracil and thyroidectomy.

pared with an antithyroid drug and operated upon (Figures 2 and 3).

(3) Those who have a mild hyperthyroidism and young patients who are good surgical risks. These can be prepared with iodine and the thyroid can be removed (Figure 4).

(4) Finally there is a group of patients who have either mild or severe hyperthyroidism but whose age, debility, or complicating diseases shorten the life expectancy. In these cases it is unwise to advise surgery when the disease can be handled indefinitely and satisfactorily by medical means (Figures 5 and 6).

Figure 1 shows an individual who has a mild hyperthyroidism with a basal metabolic rate of +30 per cent, a young woman who has a small goiter which is barely palpable. This type of patient is ideally adapted for a definitive trial treatment with one of the antithyroid drugs, and the best available at the present time appears to be propyl thiouracil.

THE TYPE of patient in Figure 2 falls into Group 2, in that she has an exophthalmic goiter, that is to say, Graves' disease, but it is a large diffuse goiter, plainly visible, and is large enough to be of cosmetic importance. There is little chance that permanent control of the hyperthyroidism and of the goiter will be effected by the use of an antithyroid drug. Preparation with one of the antithyroid drugs, followed by thyroidectomy, would be indicated in her case.

Figure 4. Large adenomatous goiter with low grade hyperthyroidism suitable for preparation with iodine and thyroidectomy.

A large nodular goiter with severe hyperthyroidism will be observed in Figure 3. Operation in such a patient, whose basal metabolic rate is over +60 per cent, would entail considerable hazard. It would not be correct to prepare her with iodine and operate on her, because the iodine would not effect a significant reduction in her basal metabolic rate or in the severity of her hyperthyroidism. This is the type of patient who should be prepared with an antithyroid drug and then operated upon. It may take a long time for this patient's hyperthyroidism to come under control.

In the presence of large adenomatous goiters, it may take months for the hyperthyroidism to be controlled with antithyroid drugs. Propyl thiouracil may fail completely, and it may be necessary to resort to methyl thiouracil or even to the parent drug, thiouracil, in spite of its toxicity, in order to subdue the hyperthyroidism associated with this huge nodular goiter. It would not be correct, however, to assume the risk of operation in aged patients who have cardiac decompensation and large goiters with severe hyperthyroidism without first completely controlling the hyperthyroidism. This principle of not operating on patients with hyperthyroidism which is not controlled has resulted in an astonishing reduction of mortality in thyroid surgery. (Figure 4.)

The patient in Figure 3 presents a little different problem, in that she has an adenoma in the thyroid which would be classified as a solitary adenoma of the thyroid. It involves only the right lobe; it is firm and is of a different consistency from the rest of the gland. The other side is normal. She has a severe hyperthyroidism, however, which makes it unlikely that this tumor in the thyroid is malignant. Hyperthyroidism and malignancy are not often associated in the same gland. Nevertheless, she has a solitary, firm, discrete adenoma of the thyroid. The presence of malignancy cannot be excluded, and it is best in these cases to prepare the patients with an antithyroid drug and remove the thyroid. After it is out the patient is always grateful because she is rid of the tumor which is large enough to be of cosmetic importance to her.

The patient in Figure 5 is old; she is a poor risk; her life expectancy is short. It makes little difference whether you advise surgery or medical treatment in this instance. This patient can just as well be treated indefinitely with propyl thiouracil. She has pernicious organic heart disease and requires medical treatment intermittently. It is not necessary to advise thyroidectomy unless the patient proves resistant to the drug.

A patient who has had three previous thyroidectomies, x-ray to the point of skin tolerance (you can see the pigmentation from the x-ray) and still has a basal rate of +65 per cent

Figure 5. Hyperthyroidism in an elderly patient with organic heart disease and a relatively short life expectancy. Indefinite treatment with propyl thiouracil justified.

Figure 6. Hyperthyroidism recurrent after two thyroidectomies and x-ray therapy to tolerance. Indefinite treatment with propyl thiouracil justified.

is pictured in Figure 6. In this type of patient the morbidity of thyroid surgery, the possibility of producing parathyroid tetany or recurrent laryngeal nerve injury, is too high to justify operation. Indefinite treatment with propyl thiouracil or the use of radioactive iodine is clearly indicated.

Subacute thyroiditis can be confused with hyperthyroidism, and these patients should not be operated upon because it will subside spontaneously in time. It may respond to use of the antithyroid drugs, and x-ray treatment in small doses will specifically relieve the symptoms within two weeks of the onset of treatment. Tenderness over the thyroid and the systemic symptoms suggestive of hyperthyroidism characterize this disease.

Hyperthyroidism in children may be of a resistant type but a trial on medical treatment may be worthwhile. On the other hand, one cannot guarantee that medical treatment is going to effect a cure because hyperthyroidism occurring in children is a severe form of the disease. Often the thyroid will enlarge and the hyperthyroidism will not be well controlled. I think it is worth a trial, but we cannot guarantee that it will work.

In conclusion, therefore, I believe that a broad

analogy can be drawn between the treatment of peptic ulcer and the treatment of hyperthyroidism. When the patient first comes to you with a peptic ulcer you do not say, "You must have a surgical operation." You do not say, either, that this certainly can be cured by medical treatment. Certain types of ulcer, obstructing ulcer, ulcer bleeding uncontrollably in spite of very good medical treatment, you know are going to require surgery. There are certain types of goiter that you know are going to require surgery. What you tell a patient when he comes in either with Graves' disease or with ulcer is "Let's give this a therapeutic trial on medical treatment; let's not make up our minds definitely until we see how this disease of yours responds to medical treatment. After that it is time to decide when surgery is indicated."

Patients with simple goiter should not be treated with the antithyroid drugs. The antithyroid drugs are goitrogens. In animals, goiter is routinely produced by the administration of these drugs. If an antithyroid drug were given to the patient here probably nothing would happen to the size of the gland, but if anything did, it would be enlargement of the thyroid.

What are the chances of malignancy occurring in such a gland? We know that many statistics have been published recently, and they are mainly surveys of autopsy material from large hospitals which show a low incidence of carcinoma of the thyroid, or figures compiled by surgeons which show an extraordinarily high incidence of carcinoma of the thyroid.

Of recent statistical surveys, one of the most striking was by Cole who showed an incidence of malignancy of the thyroid in solitary adenomas of the thyroid as high as 24 per cent. This seemed incredible to me, and I analyzed our figures and my own experience with solitary adenomas of the thyroid. I was surprised to find that if I included all malignancies of the thyroid (most of them are solitary tumors of the thyroid) and threw them into the group of solitary adenomas, the incidence of malignancy in solitary tumors was as high as 26 per cent. But there is something wrong with these figures. You know that in your practice 26 per cent of the patients who walk into your office with solitary tumors in the thyroid do not have cancer of the thyroid.

In order to try to interpret this I surveyed the incidence of goiter in patients coming routinely to the Cleveland Clinic, which, of course, is in and on the outskirts of regions of endemic goiter. The incidence of adenomatous goiter occurring in patients not coming in and presenting the complaint of goiter but coming in with chief complaints referable to other systems was 4 per cent. Approximately a fourth of these could be considered to be more or less solitary adenomas.

This means that over the same period of time that this survey was conducted, in which a certain number of carcinomas of the thyroid were found, there were about 1,300 patients who came to the clinic in whom operation was not advised at all. These patients went home and as far as we know no further difficulty was experienced with the adenomatous goiter. So the figures can be interpreted in various ways. I could say, and be statistically quite correct, that when a patient comes to my office with an adenomatous goiter with a single nodule in the thyroid, there is one chance in four that it is a cancer. Because every cancer of the thyroid cannot be diagnosed, I could tell her that there is a 5 per cent chance that the lump in the neck is a cancer.

That is an alarming figure. When a patient has a lump in her neck and one can only say that there is a 5 per cent chance that it might be a carcinoma, she will be alarmed and want to have it removed. On the other hand, I could say just as accurately, on the basis of the overall experience of the clinic, including the cases which were not operated on, that there was only one chance in 1,300 that the solitary tumor was a cancer of the thyroid. So it is a matter of the presentation of the statistics.

I do not believe that there are any adequate statistics available to date which indicate the true incidence of carcinoma in adenomas of the thyroid. That would be a difficult study to

make. Until we know what the actual incidence is, I think we are forced to disregard statistical surveys completely, whether they come from autopsy studies in hospitals or from the surgeon's laboratory. I think we must rely on clinical judgment and consider any tumor which is firm, discrete, or enlarging to be possibly malignant, and not say that every soft little involutionary nodule in the thyroid has an 8 per cent chance of being cancer.

Thousands of these patients are not even aware of lumps in their necks. Thousands of them have been told by their physicians, "There is no chance of the lump's being malignant." In thousands more the surgeon had advised against operation. All these have been disregarded in the surveys made by surgeons but should be included if the statistics are to be significant. Until we know more let us advise surgery in those patients in whom the goiters are large enough to be of cosmetic importance and those in whom clinical experience suggests the possibility of malignancy.

DAS NARRENSCHNEIDEN
Franz Hals, the Younger

DIAGNOSTIC CLINIC

Ligation of Persistent Ductus Arteriosus

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The ductus arteriosus is a normal structure which short-circuits the blood from the pulmonary artery back into the systemic circulation when the child is carried in utero. It normally atrophies and leaves as a remnant the ligamentum arteriosus. Christie, in a series of autopsies, found that the ductus normally disappears within the first three months of life and that 98.8 per cent are closed within the first year, leaving an incidence of 1.2 per cent which exist after one year of life.

Maud Abbott, in a series of 92 fatal cases of ductus arteriosus, found that the cause of death in about 50 per cent was congestive heart failure and that, interestingly enough, 30 per cent died of streptococcus viridans infection.

The clinical features of ductus arteriosus vary. Most striking is the machinery-like murmur which is heard over the entire precordium and is best heard in the second interspace on the left. This is a continuous machinery-like murmur and there is usually a low diastolic pressure.

Many investigators have pointed out that children with persistent ductus arteriosus are undernourished, but though many of them are, that is not always true. In fact some of my patients have been obese.

In 1907, Dr. John C. Monroe of Boston, in an address before the Philadelphia Academy of Medicine, described a child who seemed perfectly normal, but on straining would faint and, on several occasions, was apparently dead. The child eventually died, and on autopsy the only anomaly that could be found was a persistent ductus arteriosus. Monroe called on the pediatricians present to make the diagnosis of persistent ductus arteriosus and on the surgeons to attempt obliteration of the ductus, but it was not until May 1938 that anyone attempted the operation. Monroe worked out a technic of splitting the sternum as an approach to the ductus.

The attempt of Graybiel and Streator in a patient with a persistent ductus, who incidentally had streptococcus viridans, was made through the approach suggested by Monroe of splitting the sternum. Their patient survived the operation but died four days later, supposedly of gastric dilatation.

In August of 1938, Robert Gross of Boston first successfully ligated ductus arteriosus. Gross used a new approach that he had worked out, a transpleural approach.

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At the meeting of the American Association for Thoracic Surgery in Cleveland in July 1940, Dr. Arthur Turoff, of New York, reported four very interesting cases. He had four patients with a persistent ductus complicated by streptococcus viridans. His first patient survived the operation and was cured of his streptococcus viridans. The next two patients, as I recall, died of uncontrollable hemorrhage, and the fourth patient eventually died of streptococcus viridans.

Interestingly enough, Dr. Turoff's first patient survived the operation and was cured of streptococcus viridans. Why the patient should be cured of viridans we do not know. There have been some interesting speculations, but no one has proved them. This, of course, was in the days before penicillin. There have been some reported cases, as you all know, of the cure of streptococcus viridans by employing massive doses of penicillin.

In November of 1940 we had occasion to operate on our first ductus. This was in a child at the City Hospital. She was overweight, if anything. She had had diphtheria and was sent to the isolation hospital here. It had been known that she had a congenital lesion of some sort almost from the time that she was born. When she came into the isolation hospital with diphtheria the diagnosis of a persistent ductus was made. Because of the reports of Maud Abbott that the average age of death in patients with persistent ductus was 24 years and that they died of congestive heart failure, and because diphtheria is a noted damager of heart muscle, we suggested to the parents of this child that the ductus be ligated. The attempt was successful and the child left the hospital shortly after the operation.

In December 1940, a 14-year-old boy was admitted to St. Mary's Hospital with a low-grade fever, a persistent murmur, and a low diastolic pressure. The blood cultures were positive for streptococcus viridans. With the one successful report of Dr. Turoff of the cure of streptococcus viridans by ligation, we suggested to the parents of this boy that an attempt be made to close the ductus. The boy had as many as 800 colonies per cubic centimeter. The day before he was operated on he had 500 colonies. The day after his operation he had 3 colonies. All subsequent cultures have been negative.

Immediately after ligation the murmur and the thrill disappeared and the boy made an uneventful recovery except for a pleural effusion. This was early in our experience with the use of sulfa drugs, and because he developed an effusion we put him on sulfa drugs. His temperature went up; he had a beginning murmur, and I thought that we were in for failure. He developed a rash, and that put us on the right track; we discontinued his sulfa drugs, and, of course, his temperature and the rash disappeared, as did the murmur.

That was seven years ago. The boy is perfectly well, and the last I heard from him he had finished high school and was a candidate for the Army. I advised against military service for him, however, but I think he might even have gone through that.

We have had occasion to ligate 8 patients with a persistent ductus complicated by streptococcus viridans. Seven of them have been cured of their viridans. One of them died. The one that died I think is of interest because whenever we see a patient with a ductus the question always arises, "Is the ductus a safety valve for some other cardiac lesion and should it be ligated?" I know of no way to answer that question except to say that the incidence of other congenital lesions should not be any higher in the group with a persistent ductus than it is in normal individuals. If the patient has a machinery-like murmur of the second interspace with a low diastolic pressure, I think you are justified in exploring it.

We usually put a tourniquet around the ductus and clamp it off to see what happens to the circulation, to the murmur, and to the blood pressure. If we leave the tourniquet on for any length of time and nothing untoward happens, then we go ahead and ligate.

In the case of a 9-year-old boy who had repeated positive blood cultures for viridans, we

ligated his ductus, but his murmur did not disappear. His cultures were negative for a few days and then became positive. Someone in New York was using massive doses of the sulfa drugs for viridans. The boy had an aunt who was a physician in New York and they requested that he be transferred to New York for treatment with sulfa drugs. Since I certainly had nothing more to offer (I had ligated his ductus and his viridans continued), the boy left the hospital about a month after ligation. He still had a murmur; he still had his viridans. They arrived in New York Wednesday and the boy suddenly died on Sunday before any treatment had been given.

I was unable to get a copy of the protocol, but the parents told me that other congenital lesions were found at autopsy.

Our youngest patient was 3 years old, and the oldest was 42. We feel that the ideal age for the patient to undergo the operation is 4 or 5 years. Three is a little young; it is a little more technically difficult to do the operation at that age. We feel that these patients should be ligated before they go to school. I feel that every young child, at least, who has a persistent ductus should have it obliterated. The mortality rate from the operation is very low; the incidence of streptococcus viridans is high, and the incidence of congestive heart failure is high. I feel that it is much less of a risk to the patient to have his ductus ligated than it is to let him go on through life with it. I know that every once in a while you will see an adult who has a very large ductus and apparently had no trouble throughout life.

I feel that all children under 12 who have a persistent ductus should have it obliterated. Adults certainly should have it ligated if it is infected; they should certainly have it ligated if they show signs of congestive failure or if they show cardiac enlargement, which many do.

When performing the operation, the best landmarks are the phrenic and the vagus nerves. The incision in the mediastinal pleura is made between the phrenic and the vagus nerves, and if you follow the vagus down you find the recurrent tucked in right at the ductus, and the recurrent is the best landmark for the ductus. In the female the incision is usually made beneath the breast and the breast is retracted upward so that when the scar heals it will be hidden by the breast and will be unnoticeable.

In some of our operations we have removed a rib because it makes the closure a little easier. It is not necessary for exposure, however.

There is frequently an intercostal vein in the line of incision which we pick up and ligate. It is in the separation of the posterior wall of the ductus that we get into difficulties. If hemorrhage is going to occur, it usually occurs when we are separating the posterior wall.

Recently there has been somewhat of a controversy as to whether the ductus should be simply ligated or whether it should be severed and the two ends ligated separately. There have been some reports of recanalization of the ductus, but I think the use of the tourniquet is rather important. By clamping down the rather broad base of the tourniquet, I think that we damage the intima sufficiently and if we put on a tight suture there will be less tendency to recanalization. I have operated on 16 of these patients, none of whom have recanalized. In my cases the vessel was not severed; it was simply ligated.

Some of the untoward effects of ligation have been failure to find the ductus, ligation of the wrong vessel, infection, and hemorrhage.

DIAGNOSTIC CLINIC

Diagnosis and Management of Regional Enteritis

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ULCERATIVE lesions of the bowel have been reported in medical literature as far back as 1806 and subsequent reports are voluminous. However, it was not until 1932 that a definite clinical entity termed "regional ileitis" was reported by Crohn, Ginsberg, and Oppenheimer. They defined the disease as "a chronic, nonspecific, granulomatous, inflammatory process occupying for the most part the terminal segment of the ileum, and characterized by diarrhea, fever, obstructive phenomena, and often by fistulous tracts." These authors described the symptomatology of the disease and their concepts of the pathology, etiology, and treatment.

Many names have been given to this disease. The interest stimulated by Crohn and his coworkers produced other reports on inflammatory lesions of the bowel. It soon was recognized that the granulomatous lesions were not limited to the terminal ileum but could involve any portion of the small intestine and occasionally areas of the colon. Because any portion of the bowel may be involved, and because multiple lesions frequently are found with normal segments of bowel between, the term "regional enteritis" has been commonly adopted. After a careful review of the literature, Shapiro concluded that the term "nonspecific inflammatory granuloma" followed by the designation of the portion of the bowel involved would be an appropriate terminology for this disease. However, a more suitable name may suggest itself when the true etiology of this disease is better understood.

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ETIOLOGY

The etiology of regional enteritis is unknown. As is true in other conditions which are not clearly understood, many theories have been advanced as to the cause of this disease. It is evidently an infectious process. Whether or not the infection is secondary to some other factor such as trauma is difficult to determine. Originally, the disease was thought to be associated with appendicitis, the infection spreading from the appendix to the terminal ileum. However, in many cases of regional enteritis the appendix is not diseased. Because of the marked involvement of the mesenteric lymph nodes, this disease has been attributed to lymphatic block. The lymphatic involvement is more likely to be secondary to the infection that is associated with

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extensive ulceration and inflammation within the bowel.

Bacillary dysentery was believed to be related to this disease. Other organisms considered as etiologic factors were the tubercle bacillus, various gram-positive cocci, and bacteria of all types as well as bacterial toxins. A theory of relationship to lymphogranuloma inguinale has been advanced. A clinical similarity to certain virus diseases and the profusion of eosinophiles in regional enteritis have suggested the possibility of a virus etiology. Achylia gastrica has been considered as a related condition because of the absence of disinfecting power of hydrochloric acid and gastric juice. However, many patients with normal or increased gastric acids develop regional enteritis.

Many other factors have been suggested as being responsible for or contributory to this disease. They include allergy, interference with the blood supply, the presence of foreign bodies in the bowel, trauma, and heredity. There is reason to believe that overdistention of the bowel, to a degree of damage to the mucosa sufficient to permit the intestinal flora to penetrate the bowel wall, may be followed by ulcerative lesions.

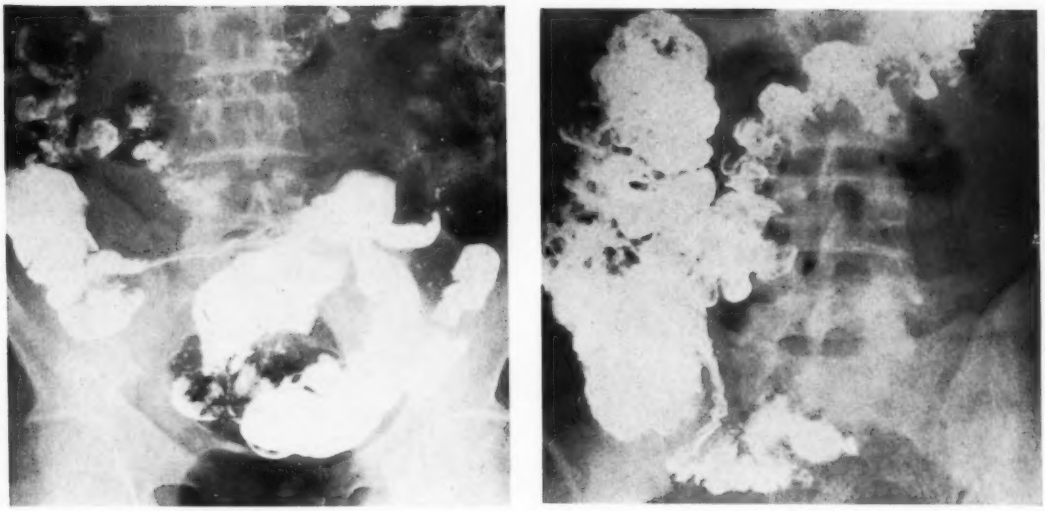
SYMPTOMATOLOGY

The signs and symptoms of regional enteritis vary with duration of the disease and the stage in which the patient is first seen. Although all patients do not run identical courses, the description of four stages by Crohn will apply to a high percentage of individuals suffering with this condition. These stages are as follows:

(1) Acute or surgical abdomen. The disease often begins with acute manifestations suggestive of appendicitis. This is evidenced by the fact that approximately 50 per cent of patients in the early stages of regional enteritis are operated for appendicitis. They present signs and symptoms of peritoneal irritation most frequently in the right lower quadrant. Fever, leukocytosis, tenderness, muscle spasm, and diarrhea often accompany the onset of the disease. Not all patients have an acute episode at the onset. Many have a slow, progressive development of symptoms.

(2) Symptoms of ulcerative enteritis. In this stage of the disease the patient complains of colicky abdominal pain. A low grade diarrhea with blood and mucus in the stool associated with a slight elevation of temperature, progressive weight loss, anemia, and weakness are common. Tenesmus is a rare complaint. Low abdominal tenderness frequently is present and a palpable mass may be noted in the right lower quadrant or in the lower abdomen. The presence of a mass is indicative of mesenteric involvement.

(3) This is a stage of chronic incomplete intestinal obstruction and is brought about by gradual stenosis of the bowel. In some patients this is the first manifestation of the disease. Symptoms frequently consist of abdominal cramps, borborygmus, visible peristalsis, distention, and occasional vomiting. Constipation may replace diarrhea. The general debility of the patient is progressive. A palpable mass in the lower abdomen usually is present.



Figures 1 and 2. The string sign of Kantor as demonstrated by barium enema.

(4) This is a stage of chronic fistula formation as well as other complications. A variety of complications including obstruction, perforation, development of abscesses, and the establishment of fistulas may result. Internal fistulas between various loops of bowel, between the bowel and other hollow viscera, or between the bowel and the abdominal wall, perineum, or pelvic organs may occur. Perirectal abscesses and fistulas secondary to regional enteritis have been reported in 15 per cent of cases.

In all stages of the disease, blood is present in the stools and produces a high incidence of secondary anemia. Occasionally, massive hemorrhage occurs.

DIAGNOSIS

Diagnosis of regional enteritis can be made clinically, radiologically, and surgically. In the acute stage it may be made only by exploratory laparotomy. In the subacute and chronic stages it may be made by x-ray examination alone when the essential roentgen finding is a stenosis of the terminal ileum resulting in the typical "string sign" of Kantor. This sign can be demonstrated in most cases by barium enema alone as a result of the reflux of the barium through the ileocecal valve. (Figures 1 and 2.)

Occasionally, careful studies of the small bowel are necessary. This is accomplished by giving the patient swallows of thin barium and making x-ray studies of the small bowel at hourly intervals for six to fourteen hours. (Figure 3.) This technic frequently will visualize multiple areas of constriction and dilatation in the course of the small bowel. (Figures 4 and 5.) Other roentgen findings are constant nonvisualization of the involved segment in some cases, dilatation of the intestine proximal to the involved segment, deformity of the cecum, and displacement of the normal intestine by a mass in the right lower quadrant. The absence of a normal barium shadow in the proximal colon was described by Stierlin in 1911 and this has since been known as Stierlin's sign. It was considered indicative of tuberculosis but any ulcerating granuloma of the ileocecal region can have a similar roentgen appearance.

Figure 3. Regional enteritis of terminal ileum demonstrated by thin barium given by mouth.

DIFFERENTIAL DIAGNOSIS

The three most important diseases to be differentiated from regional enteritis are appendicitis, tuberculous enteritis, and ulcerative colitis. Others are diverticulitis, amebiasis, sarcomatosis of the small intestine, nontropical sprue, Hodgkin's disease, and foreign bodies.

The differential diagnosis between regional enteritis and appendicitis already has been discussed. The signs and symptoms may be identical except for the presence of diarrhea in the former. In regional enteritis the white blood cell count is usually higher than that found in the typical case of appendicitis, reaching as high as 20,000 to 25,000. The elevation of temperature in the acute stage usually is higher than that found in appendicitis. In about one-half of the cases the differential diagnosis can be made only at operation. In the subacute and chronic stages the differential diagnosis is more obvious because of the signs and symptoms of partial bowel obstruction, the duration of the disease, and the presence of weakness and loss of weight.

In nearly every case of tuberculous enteritis, pulmonary tuberculosis is present. The case in which evidence of pulmonary tuberculosis is lacking is rare. Tuberculous enteritis seldom results in partial bowel obstruction and in most cases its presence is manifested only by diarrhea. X-ray examination of the gastrointestinal tract will not differentiate between the two conditions, nor will the gross pathology noted at surgery. Microscopically, one will find the typical tubercle in tuberculous enteritis.

Occasional association of regional enteritis and nonspecific ulcerative colitis makes differentiation difficult. A common pathogenesis may be found for the two conditions. In most cases, however, one can distinguish between the two by proctoscopic examination and barium enema. In the uncomplicated case of regional enteritis, proctoscopic examination will reveal a normal colon, whereas the typical picture of ulcerative colitis will be observed in the latter condition. There is no small bowel pathology in the usual case of ulcerative colitis as shown on roentgen examination. The diagnosis of diverticulitis also can be made on roentgen examination.

Amebiasis may be diagnosed by examination of the stool and proctoscopy, but x-ray examination may be of little diagnostic value.

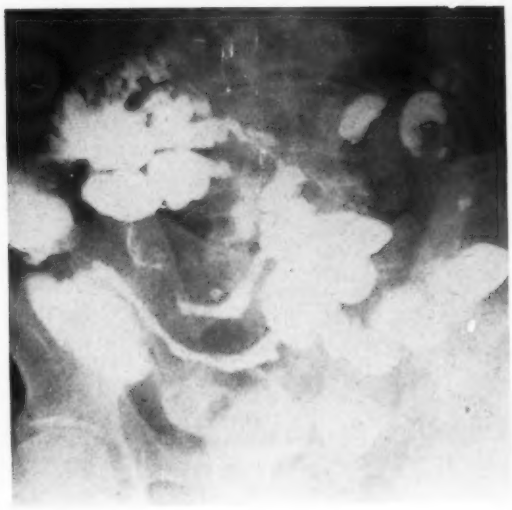
Sarcomatosis of the small intestine is rare but occurs frequently enough to warrant consideration. The differentiation is made by exploratory laparotomy and histopathologic studies.

Nontropical sprue is distinguished by the appearance of the stool. Hodgkin's disease is characterized by systemic manifestations, presence of lesions extrinsic to the small bowel, and by its microscopic appearance.

PATHOLOGY

At operation in the acute stage the terminal ileum or involved segment of small intestine may reveal only an edematous, reddened, granular serosa. Usually there is a little serosanguinous fluid within the peritoneal cavity.

Later there will be numerous stringy adhe-



Figures 4 and 5. Multiple areas of constriction demonstrated by barium studies.

sions resulting in a matting together of several loops of small intestine. The appendix or cecum may be involved in this process. There is always a striking mesenteric lymphadenopathy and thickening of the mesentery. (Figure 6.)

When more than one segment of bowel is involved the intervening intestine and mesentery usually appear normal. This situation has given rise to the term "skip areas." In the chronic stage, scar tissue may cause partial or acute bowel obstruction with dilatation of the proximal bowel. The diseased bowel may be greatly thickened and "garden hose" in character. The mucosa presents small ulcerations along the mesenteric border and much folding and overgrowth as a result of the contracting scar tissue. This markedly diminishes the lumen and accounts for the characteristic x-ray appearance.

Microscopically the picture of regional enteritis is one of chronic inflammation and chronic lymphedema. There is marked fibrosis and thickening of submucosal and mucosal layers. (Figure 7.) The entire structure of the bowel wall may show a mononuclear infiltration with a preponderance of these cells in the mu-

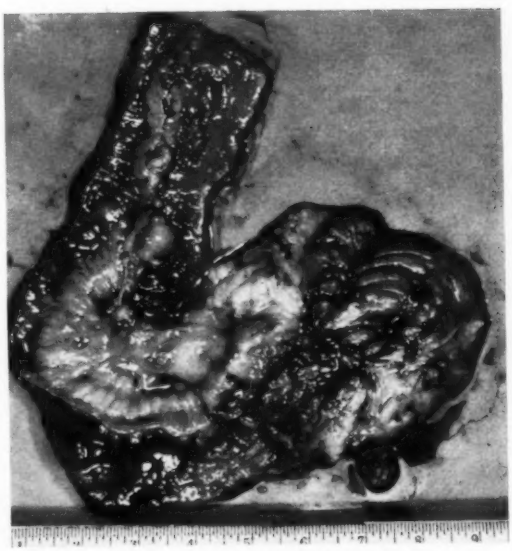
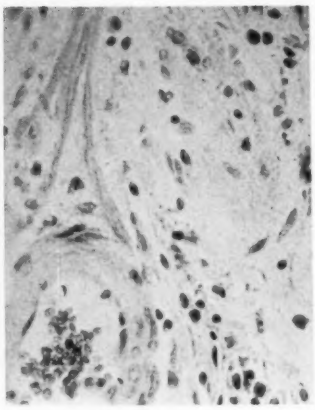


Figure 6. Photograph of segment of small intestine showing ulceration of mucosa, thickening of the bowel wall, edema of the mesentery and lymphadenopathy characteristic of regional enteritis.



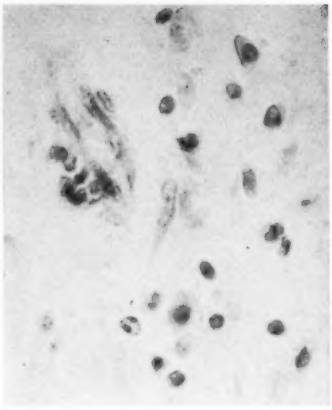


Figure 7 (left). Cross section of bowel wall in regional enteritis showing marked thickening. Figure 8 (center). Histologic picture of bowel wall in regional enteritis showing monunuclear infiltration. Figure 9 (right). Giant cells seen in regional enteritis.

cosal layer. (Figure 8.) Giant cells are commonly seen and have been responsible for the erroneous assumption that the disease is of tuberculous origin. (Figure 9.)

MANAGEMENT

Undoubtedly, many cases of uncomplicated regional enteritis subside spontaneously or respond to conservative therapy. It is my opinion that many such cases occur but are not diagnosed. If such cases are recognized and do not develop surgical complications, conservative therapy may be justifiable. However, when complications do develop, surgical therapy should be promptly administered. As the etiology of the disease is undetermined, no specific nonsurgical remedy is known. General supportive care accompanied by a nonirritating diet is important. Our experience with the use of various antibiotics including the sulfa drugs, penicillin, and streptomycin has not been encouraging and has shown no improvement over conservative therapy without the use of these drugs.

In the acute stages of this disease the diagnosis often is established by abdominal exploration, usually because of the mistaken diagnosis of acute appendicitis. If this occurs and the appendix is found to be uninvolved it should not be removed because of the danger of fistula formation. If an exploratory operation reveals an uncomplicated acute regional enteritis and the patient has not been prepared for intestinal surgery, radical surgical procedures should be delayed until the disease has become more chronic and the patient has been adequately prepared. In the past, resection of the entire diseased portion of the affected bowel and mesentery has been advocated. This carries a fairly high mortality rate and is followed by frequent recurrence of the disease in spite of the radical nature of the procedure. Ileotransverse colostomy has been utilized, anastomosing the ileum proximal to its highest diseased portion to the transverse colon. When the ileum distal to this anastomosis has not been divided, good results have been infrequent. This operation often is followed by an extension of the disease in the small bowel and to the colon in the region of the anastomosis.

Ileotransverse colostomy with exclusion of the ileum distal to the anastomosis has proved to be a very satisfactory procedure. Garlock has reported a series of nearly 100 patients on whom this operation was performed with no mortality

and with a high incidence of remission of the disease. He reported spontaneous healing of fistulas in almost all cases where this complication existed by this more conservative operation of ileotransverse colostomy and exclusion of the ileum. Such results support preference of this procedure over radical surgical treatment of abdominal fistulas and extensive resection of diseased bowel segments.

CASE REPORT

The patient who has kindly consented to appear before you today is a doctor of dental surgery. As is so common among professional people, he not only has developed an uncommon disease but also has developed numerous complications and an unusually extensive bowel involvement. Dr. G., who is 37 years of age, informs me that when he was a young lad he was kicked in the abdomen by a horse. He was confined to bed for a few days. Following this accident he developed abdominal pain and discomfort whenever he attempted strenuous athletic training. The history of this injury is of interest because of the frequent mention of abdominal trauma as an etiologic factor in cases of regional enteritis.

In 1931, at the age of 20, Dr. G. first noted mild indigestion accompanied by belching and abdominal tenderness. His symptoms were not severe at this time. Medical investigation failed to reveal the nature of his illness. One year later severe abdominal pain occurred the day following an unusually heavy evening meal. The pain was intense and diffuse and spread throughout the entire abdomen. He was considered a surgical emergency with a diagnosis of peritonitis and was immediately operated. At this operation the ileum was found to be spongy, inflamed, and dilated and evidently had ruptured producing a diffuse peritonitis. The abdomen was drained but no bowel was removed or repaired. His postoperative convalescence was complicated by abdominal drainage, hiccoughs, and vomiting. At the end of six weeks his drainage had ceased and he was sufficiently improved to be discharged from the hospital. He was symptom-free for a period of four years, during which he had no pain and had gained in weight to a maximum of 175 pounds. He then developed cramping pains immediately after meals. His description of the pain is quite typical of that seen in the early obstructive stages of regional enteritis. Weakness and weight loss were progressive. Diarrhea, which usually is seen in this disease, was not noted.

In 1935 a diagnosis of regional enteritis was established and he again was operated. In a two-stage procedure an ileotransverse colostomy was performed with removal of a portion of the terminal ileum and right colon. An abdominal fistula followed this operation. Four subsequent operations were performed in an effort to close the fistula but all were unsuccessful. In 1936, after the removal of more small intestine, the fistula healed.

The patient was symptom-free from 1936 to 1942 when he had a recurrence of typical symptoms of regional enteritis. He was reoperated and because of extensive involvement of the small bowel, his entire ileum and all but approximately 3 feet of jejunum were removed. Therefore, this patient is now living with only 3 feet of small intestine and with only the left half of his colon still present. In spite of the small amount of bowel remaining, this patient whose weight fell to 96 pounds in 1942, has gradually gained to his present weight of 140 pounds. When he was questioned today the following information was obtained: He is able to eat all types of food except raw vegetables, particularly onions and radishes which produce heartburn and indigestion. He has four meals a day and develops hunger if he does not eat every three to four hours. Although he indulges in little physical activity, his appetite is excessive and he states that he eats far more food than the average hard working man.

The patient has an average of four to five stools each day and if the daily bowel movements are less, he has a feeling of constipation. The stools are soft and fetid, with considerable fermentation.

It is apparent that this patient, due to the small amount of remaining intestine, does not thoroughly utilize the food which he eats but by the ingestion of large amounts of concentrated food he is not only able to maintain an adequate state of nutrition but has gained 45 pounds. However, two years ago he developed what was diagnosed as pernicious anemia which is being treated by the injection of liver extract.

This patient has had a total of eleven operations for regional enteritis and its complications. Since his last operation in 1942 he has had no pain or other symptoms suggestive of a recurrence of the disease. He is able to carry on his practice and states he can lead a fairly normal life with few restrictions. He has asked the question "Might I get this disease again?" That question cannot be answered with certainty but after five years of freedom from symptoms, prospect of a permanent cure is encouraging.

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DIAGNOSTIC CLINIC

Diagnosis and Treatment of Myasthenia Gravis

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MYASTHENIA gravis is a somewhat rare disease—not quite so rare as we thought it was ten years ago, but still a disease of which there are probably not more than 1500 cases in this country. It is a simple disease in one sense of the word, for it is characterized by a weakness of muscular action entirely due to excessive or pathologic fatigue. That is the only symptom of myasthenia gravis. It might be said that it is an exaggeration of normal fatigue of voluntary muscles, because in each case where the muscle is fatigued it will return to normal, or nearly normal, on rest, exactly as muscles return to normal after they are fatigued in normal persons. It is important, I think, to grasp the fundamental concept of this disease because it simplifies the whole problem in that you have only one possible symptom, namely, fatigue of some voluntary muscles.

The interest in the disease lies partly in the fact that certain groups of muscles are likely to be involved at the beginning and there may be a shifting from one group to another. The disease, moreover, progresses by spontaneous remissions and relapses. It covers a long period of time. Up to about 1935 the mortality was between 50 and 75 per cent, so its name, "grave myasthenia," was indeed justified. I have estimated that in one hospital where I am working, over a period of thirty years prior to 1935 we had only 30 cases, one a year, and that half of those cases died in the hospital and another half died within a year after leaving the hospital. This was indeed a fatal disease.

The mortality from the disease at the present time, however, is probably less than 10 per cent, so that we have reduced the death rate from roughly 50 to 75 per cent down to less than 10 per cent.

Myasthenia gravis has been well known for many years. As a matter of fact, it was described even in the seventeenth century. The two names that stand out in the nineteenth century are Erb and Goldflam.

The original paper of Erb was published in 1879, while Goldflam's first report appeared in the year 1893.

By 1900 the disease was well recognized clinically.

When we consider the number of cases that we have seen since 1935—since which time we have had a method of diagnosis and a means of alleviation of symptoms—the incidence has in-

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HENRY R. VIETS

creased greatly. At the Massachusetts General Hospital, for instance, from 1905 to 1935 we had this scattering of cases that I have already mentioned. Since 1935 we have seen more than 200 cases. That means a number of things. Our interest in the disease has increased; more cases are being discovered because we have an adequate diagnostic test; and the number of cases that survive over a long time has increased because they do well under treatment.

I doubt whether there are any more cases in the United States today than there were ten or fifteen years ago, but a lot more have been discovered than formerly. That is the very point of this paper, because I want to show you how such cases can be discovered and how these patients can be treated.

The presenting symptoms of the disease vary a good deal. There is always a fatigue of voluntary muscles, but early in the course of this disease certain muscles are more easily fatigued than others. When we analyze the histories of our patients, we see that the muscles that have to do with movement of the eyes and eyelids are most frequently affected. In a little over 45 per cent of the cases the first symptoms often are ptosis and diplopia. Most of these patients, therefore, go to the ophthalmologist, though they may be seen first by the general practitioner. If you have this disease in mind—which unfortunately many physicians do not—you will consider seriously the possibility of myasthenia gravis when you have a patient with a sudden ptosis and double vision without obvious cause, the symptoms fluctuating during the day or during the week or month, and usually being better in the morning after a night's rest and worse in the afternoon.

THE SECOND group is even more important because they have no distinctive and outstanding muscle signs such as ptosis and diplopia which you see as soon as the patient comes into your office, but they come in on account of general weakness, fatigue in walking upstairs, difficulty in raising their arms and doing ordinary household tasks. This is the large group, about 30 per cent of the total, that have general muscular weakness and is confused most often with cases of neurasthenia. It is probably the group that is less often diagnosed than the cases with special symptomatology such as ptosis and diplopia.

Another group, comprising about a fifth of the cases, have dysphagia and dysarthria. Here again there is a fluctuation in the symptom—the patient may have no trouble in swallowing breakfast but will have difficulty with luncheon and increasing trouble with supper. Speech is affected the same way: after a few minutes the voice becomes nasal, and always on rest there is a tendency to restoration of function to normal. That is the key of the whole disease.

There is still another group in which neck weakness is an important feature and is sometimes the only symptom. A patient will notice suddenly one morning on washing his face in the bowl that he will start to lift up his head and he will be unable to do so. If he rests a

few minutes he can lift his head normally.

Thus the ophthalmologist may see the ptosis and diplopia cases; the laryngologist may see the dysphagias and dysarthrias; the general weakness group usually falls to the general practitioner, as does the group affected only with neck weakness; but any of them may be seen by anyone at any time.

Let us look at the age group, which is another important point. You will find in the textbooks that for many years everyone thought this was a disease of young people, of adolescence or the third decade of life. It is in part, but when we come to analyze our cases they spread all the way from the very earliest years of life to well into the eighties, and interestingly enough there is a large group of patients between 60 and 70 which we had never discovered before. These are the cases that in the past were almost inevitably missed in diagnosis because they were confused with the patients who at that age have obstructions of the larynx due to cancer, bulbar palsy with speech defects, vascular changes in the brain stem, and other diseases of a degenerative type. The superintendent of a hospital began to have his first symptom when he was over 70, and I must say the diagnosis was missed for five or six months because ten years ago we were not thinking in terms of this disease. One should look at the older age group as a very important and formerly undiagnosed group of patients with this disease.

When we put those groups into decades, it is clear that the disease may appear in any decade during the patient's life except perhaps over 80 and rarely under 10. A few cases occur in infants. I have not personally seen any, but there are some in the literature. It is possible that those are cases of myasthenia gravis, but it is not easy to be sure. The patients most frequently seen are young adults or people in middle life.

Between 1930 and 1935 we had developments in our knowledge of this disease which revolutionized our whole attitude toward it. In 1931 Aeschlimann and Reinert were investigating physostigmine and were making up synthetic analogues. One they called prostigmine now known as neostigmine. This drug proved to be invaluable for it turned out to be a diagnostic as well as a therapeutic agent for the disease. It is the only drug that has any marked effect upon myasthenia gravis. There are others that have some effect, but this is *the* drug that has the most marked effect and the one that is used as a diagnostic test.

As a diagnostic test, the dosage is 1.5 mg. of neostigmine methylsulfate given subcutaneously. The methylsulfate is the soluble form put up in an ampule, and to that is added some atropine to overcome the intestinal stimulation which often goes along with the initial use of the drug. There is a diagnostic ampule now available containing the proper dose for an adult and the proper amount of atropine in one ampule. If there is reasonable doubt in your mind regarding the diagnosis in the early stages, one should attempt either to confirm or to discard the diagnosis with a diagnostic test using neostigmine.

There may not be reasonable doubt about the diagnosis if you are familiar with the disease, because the symptomatology is so definite, so unique, and so characteristic that a patient having a muscular weakness that recovers to normal after a period of rest and then relapses on effort is not found in any other disease. With a good history and a knowledge of the background of this disease in mind, the diagnosis is usually exceedingly easy from the clinical record alone. On the other hand, if you are not thinking about the diagnosis, and if you consider the disease to be a rare one, you need some sort of reinforcement of a presumptive diagnosis of myasthenia gravis.

Neostigmine is found to be an almost specific remedy in the diagnosis and treatment of this disease. It overcomes in large part the one principal symptom, namely, muscular weakness, and because of that we use it as a diagnostic agent. If a patient has ptosis, diplopia, facial weakness, difficulty in chewing, difficulty in talking, or difficulty in swallowing, and the

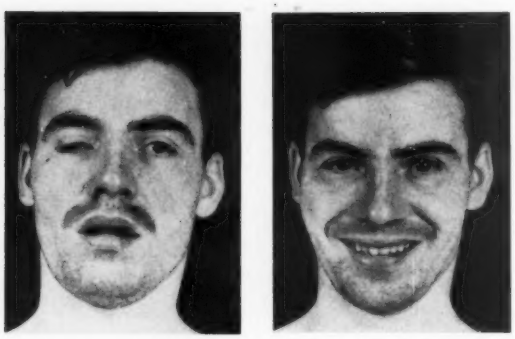


Figure 1. Prostigmine diagnostic test. Alleviation of symptoms after injection of 1.5 mg. of prostigmine methylsulfate plus 0.6 mg. of atropine sulfate ("the diagnostic ampule"). The patient, aged 32, had had symptoms for over two years. Since 1940, when the diagnosis was first made, the patient has been fully adjusted on 4 to 6 tablets of prostigmine bromide, 15 mg. each, taken by mouth.

drug is injected subcutaneously in the appropriate amount as given in the diagnostic ampule, the patient will, in about 20 to 30 minutes, recover entirely, or in very large part, all use of the affected muscle. It is perhaps one of the most dramatic changes that we see in all medicine.

Figure 1 illustrates this response to the drug. This patient had dysarthria and dysphagia, ptosis and diplopia. I think you can see the bilateral facial weakness. That is a typical picture of myasthenia gravis with the facial and cranial muscles involved. Fifteen minutes after the injection of neostigmine the whole picture is changed—the ptosis disappears; the diplopia is gone; the facial muscles are now in action; chewing, swallowing, and talking are normal, and the diagnosis is unmistakable. No other disease responds in this remarkable way. Other diseases may give a slight response, but certainly under 10 per cent, whereas the response in myasthenia gravis runs up to 85, 90, or even 100 per cent as in this picture. Therefore the diagnosis is clinched if this response is present.

This test was first reported in 1935 by Dr. Schwab and myself, and I think that in the twelve years that have elapsed it is fair to say it has been accepted as a diagnostic test. As we have used it in more than 200 patients I think that we were never in doubt in regard to the diagnosis of myasthenia gravis if the response was in the 85 to 90 per cent group; if it was down below 25 per cent, there was a reasonable doubt about the diagnosis, and most of those cases do not turn out to be myasthenia gravis. It is, therefore, a sound test. If you use it and the response is good, the diagnosis cannot be anything but myasthenia gravis.

We also have another method of diagnosis in certain cases which is very satisfactory. If the patient has dysphagia as one of the symptoms, you can study that difficulty in swallowing under the fluoroscope with an ordinary barium meal, and then after injection of neostigmine, you will find in 20 to 30 minutes that the swallowing reflex is absolutely normal. Here again it is a dramatic test for the disease and it is unmistakable; no other disease could possibly do this. In this way you differentiate myasthenia gravis from all the other diseases causing difficulty in swallowing. Should your patient have dysphagia as one of the symptoms or as the principal symptom, this study under the x-ray before and after neostigmine will make the diagnosis quite certain.

As for the treatment of the disease, the first drug that was used to any extent was ephedrine. Dr. Harriet Edgeworth, in this country, showed as early as 1930 that this was of some value, and it is still of some use. It falls into the group of about 10 to 15 per cent of usefulness compared with neostigmine which is 85 to 90 per cent in its usefulness.

Then Dr. Mary Walker, a London physician, first used physostigmine in 1934. Physostigmine was soon replaced by neostigmine, which is an easier drug for the patient to tolerate and has practically no side reactions of the type associated with physostigmine.

Neostigmine is used in two ways. In the diagnostic test it is always used subcutaneously. In the treatment of patients it may be used either subcutaneously or orally. All our patients

take the medicine orally in the form of prostigmine bromide, the only tablet made for oral medication. There are 15 mg. of neostigmine bromide in each tablet.

Under certain conditions we may supplement the oral dosage with subcutaneous injection, but that is rarely done, and not more than 2 or 3 per cent of my patients take the drug subcutaneously. They are all adjusted to oral neostigmine bromide.

Theoretically this is the only possible way to treat a patient with a chronic disease that requires the administration of a drug for a period of months, years, or even possibly the rest of his life, because neostigmine treatment turns out to be a form of substitution therapy. Something has dropped out of the body, there is a chemical dysfunction at the junction of the nerve and the muscle; neostigmine is added to this myoneural junction or synapse and the chemical reaction is restored to normal, or partially so. One must think of this as a form of substitution therapy exactly as one thinks of insulin in diabetes or liver therapy in pernicious anemia.

That point is a very important one, because the minute you grasp it your whole attitude toward this disease is changed. The treatment of this disease becomes a life problem. Success can be reached only if the patient is continually under the doctor's care or observation, presumably for the rest of his life. To be sure, he may have long periods of remission in which he takes no medicine and has no symptoms. Some of these remissions have lasted for an extraordinary length of time, even as long as twenty years. Most of the remissions, spontaneous in type, last perhaps six months or a year; some of our recent remissions have lasted five years. But in spite of that one must consider the patient as one to be continually under therapy.

REMISSIONS IN TWO CASES OF MYASTHENIA GRAVIS IN WHICH PROSTIGMINE WAS REQUIRED TO CONTROL SYMPTOMS

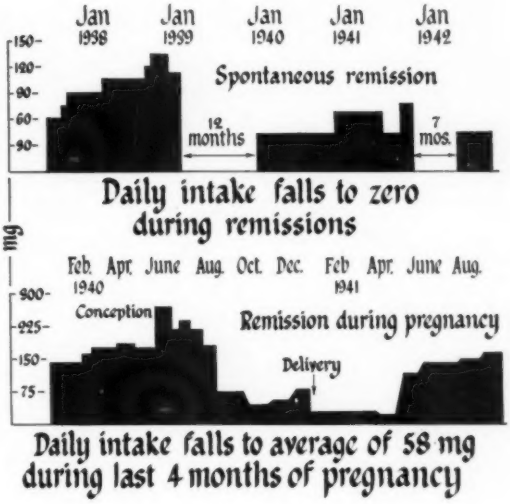


Figure 2.

A BRIEF discussion of the thymus in relation to this disease is of importance. It was noted at post mortem, before the days of modern treatment, that the thymus was changed in a person who had myasthenia gravis. In about 50 per cent of the cases hyperplasia was found, in some cases tumor formation, or thymoma. That led to an investigation of the relationship, if any, between the thymus gland, so-called, and myasthenia gravis. It is obviously a difficult problem. We are dealing with a structure that we know little about; we do not actually know whether it is a gland (particularly in the adult), whether it has any hormonal secretion, or what possible relationship it could have to this disease. Those matters are still uncertain. The observations on the thymus at post mortem led, however, to the surgical removal of the thymus gland or thymoma in a certain number of patients in recent years. One series in England has reached 100, and in this country some physicians have removed at least 50, others 20. I suppose there are 250 patients that have had thymectomy.

WHAT ARE the results of thymectomy? They are difficult to evaluate. Here you are dealing with a disease that has spontaneous remissions and relapses. A patient may do very well and even have a "cure" in the sense that he has no symptoms and needs no neostigmine after thymectomy. On the other hand, for each patient who has had a thymectomy I can show three patients from my clinic who have not had a thymectomy who do exactly as well. So you see that is a difficult problem to resolve. I am still not in a position to tell you whether thymectomy is of value in this disease or not, and I think that is the general consensus in this country. It is not necessarily the way people feel throughout the world. But I should like to say that we are still in the experimental stage as far as thymectomy is concerned. I rarely advise it. I advise it only in patients who have not done well under their medical treatment, and that, I think, is justified.

TABLE 1

STATISTICAL SUMMARY

MYASTHENIA GRAVIS CLINIC (1935-1946)

	NUMBER	PER CENT
Cases diagnosed since 1935	200	
Deaths since 1935		20
Patients living, December 31, 1946	159	
Excellent adjustment on treatment		52
Good adjustment on treatment		39
Poor adjustment on treatment		9
Partial remissions		17
Complete remissions		14

AGE AT ONSET OF SYMPTOMS OF 200 PATIENTS WITH MYASTHENIA GRAVIS

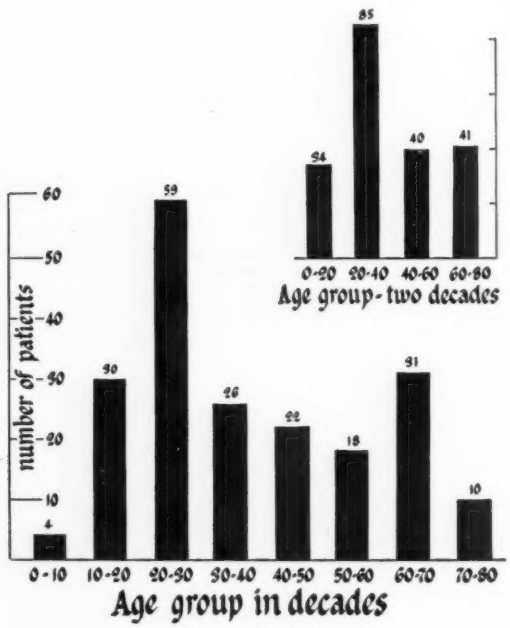
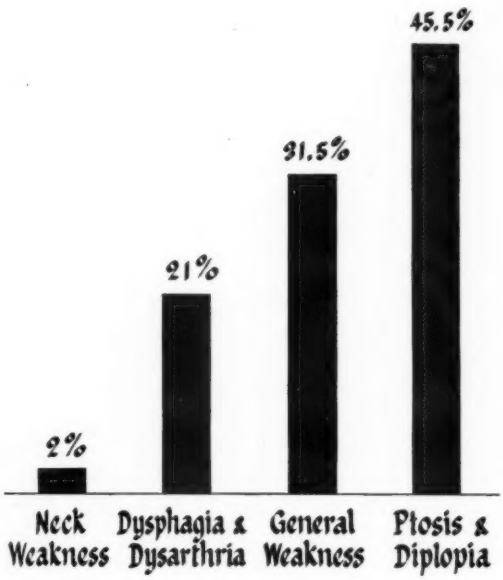


Figure 2 shows the spontaneous remissions that occur. The chart is based on the amount of neostigmine that the patient takes. There is a twelve-month period in the top chart showing the record of a patient without any symptoms and with no need for medicine. Then a relapse occurs, and there follows a seven-month remission. Remission often happens during the last two trimesters of pregnancy. The remission may last for a number of months after pregnancy is terminated.

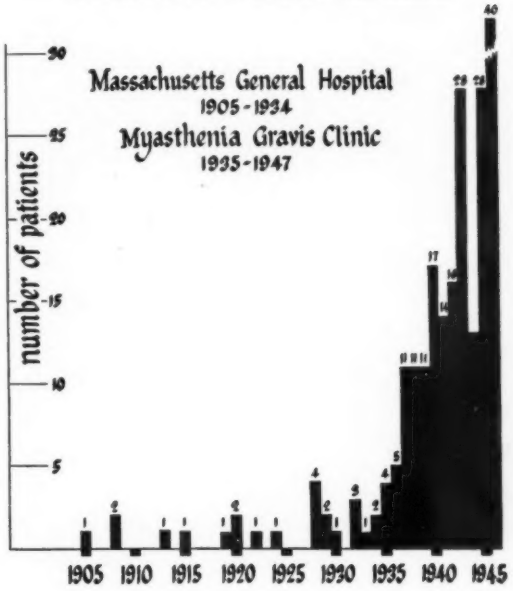
A general summary of the clinic cases shown in Table 1 gives you an idea of how things are going at the present time: 200 patients with a 20 per cent death rate since 1935. I told you the mortality was probably under 10 per cent. You must realize that in this age group, which goes up to 80 years, there is a natural mortality on account of age, so I think one ought to reduce the mortality under modern treatment to 10 per cent. Half of the patients are well adjusted on treatment; another group has good adjustment; some, about 10 per cent, have poor adjustment, which is the best we can do. Partial remission occurs in 17 per cent; complete remission in about 15 per cent.

The following case of a woman patient shows an interesting history. For ten years, since she was 32 years of age, she was almost bedridden, at least houseridden. She could get up and do a little work, she could raise her arms slightly, but for most of the time she was con-

PRESENTING SYMPTOMS IN 200 PATIENTS WITH MYASTHENIA GRAVIS



CASE INCIDENCE OF MYASTHENIA GRAVIS



fined to bed. A few months ago her doctor began to think of myasthenia gravis as a possible diagnosis. An injection of neostigmine was given and in 15 or 20 minutes the patient got up out of bed, walked around, raised her arms, and was almost normal. It is extremely interesting that for ten years a patient should be allowed to go undiagnosed with a disease that has such remarkable possibilities from therapy. She has begun to be adjusted on oral neostigmine. At the present time she is taking 6 tablets a day, one at 5:00, one at 7:00, one at 10:00, one at 12:00 noon, one at 5:00 and one at 10:00. This she has done for three months, and during that time she has been able to be up every day, drive 20 miles in her automobile, and be in reasonably good condition.

I have an idea that she is not quite fully adjusted on treatment as yet. The average intake in my clinic is not 6 or 7 pills a day, but nearer 10 or 12 a day. If that amount is given and if the lateralization of the dose is correct throughout the day, a patient ought to be practically free from symptoms at all times. One does not reach that height always, but that is the aim—to balance the neostigmine against the symptoms of the disease and to make the patient as well as possible. I have five or six doctors with myasthenia gravis, and I am glad to say they have all continued in practice, although under a somewhat modified schedule.

SCIENTIFIC EXHIBIT

Diagnosis and Treatment of Bronchial Asthma

LEON UNGER, M.D., HERMAN A. LEVY, M.D., ALBERT H. UNGER, M.D., AND ISABELLE B. EISELE, M.D.

NORTHWESTERN UNIVERSITY MEDICAL SCHOOL AND WESLEY MEMORIAL HOSPITAL, CHICAGO

DIAGNOSIS

Bronchial asthma is an allergic condition characterized by wheezing, dyspnea, orthopnea, cough, associated with rhinitis and partial obstruction of lower air passages. Most cases: (a) history previous attacks, allergy in family or other allergies in patient; (b) generalized wheezing and prolonged expiration; (c) eosinophilia in blood and especially in sputum; (d) relief from epinephrine and/or aminophylline; (e) positive skin tests. Any one finding can occur in nonallergic conditions.

Complications

Chronic asthma leads to emphysema and deformed chests. Bronchitis, sinusitis, pneumonitis, atelectasis, and spontaneous pneumothorax may occur.

Differential Diagnosis

From all other causes of dyspnea, wheezing and cough, e.g., acute cardiac dyspnea, fibroid tuberculosis, silicosis, substernal goiter, lung carcinoma, foreign bodies. Inspiratory wheezing indicates obstructive condition; rare in bronchial asthma.

Causes of Attacks

Often easily discovered, but in some cases every diagnostic method is used; (a) careful history; (b) relief or return of symptoms by avoidance or exposure to cause, e.g., dog hair, egg; (c) relationship of symptoms to atmospheric pollen or mold counts; (d) skin tests, scratch and intradermal, clinically corroborated.

TREATMENT

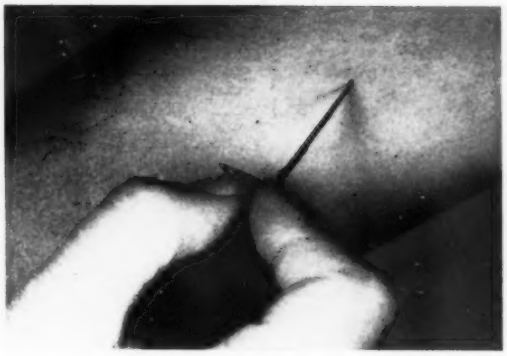
Preventive: (a) Children of allergic parents: avoid pets, orris root, feathers, excess house dust and pollen. Add new foods singly. Prompt allergy survey if "eczema," "bronchitis," rhinitis, hay fever, or wheezing are present. (b) Allergic persons: avoid dusty occupations: farmer, baker, furrier, miller, domestic.

A national campaign for education in and prevention of asthma is a *must*.

Specific: (a) *Avoidance* of allergens, e.g., dog, orris root, house dust. May be sufficient. (b) *Hyposensitization:* injections of increasing amounts of extracts of important allergens which cannot be avoided, e.g., house and occupational dusts, pollens, molds, orris root. Results usually good.

Symptomatic: (a) Reassuring patient most important single measure. (b) Epinephrine: subcutaneous 1:1,000; intramuscular 1:500 in oil; by inhalation 1:100 spray. (c) Aminophylline: 3¾ to 7½ gr. intravenously; 10 gr. in water, or 7½ gr. suppository rectally. (d) Ephedrine: ⅜ to ½ gr. orally. (e) Glucose: liter 5 per cent intravenously with aminophylline. (f) Air-filtered, dust-free room (hospital or home). (g) Iodides, apomorphine, syrup ipecac, mild sedation. (h) Do *not* use *morphine*—too dangerous. (i) Penicillin or sulfonamides for infectious complications; little effect on asthma itself. (j) Vaccines, x-ray therapy, removal foci infection, bronchoscopy, psychotherapy, estrogens.

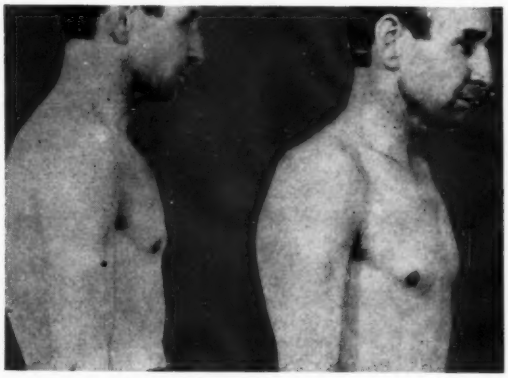
Technic of intracutaneous test (tuberculin syringe, 27 gauge needle).



Technic of scratch test (forearm, cataract knife).

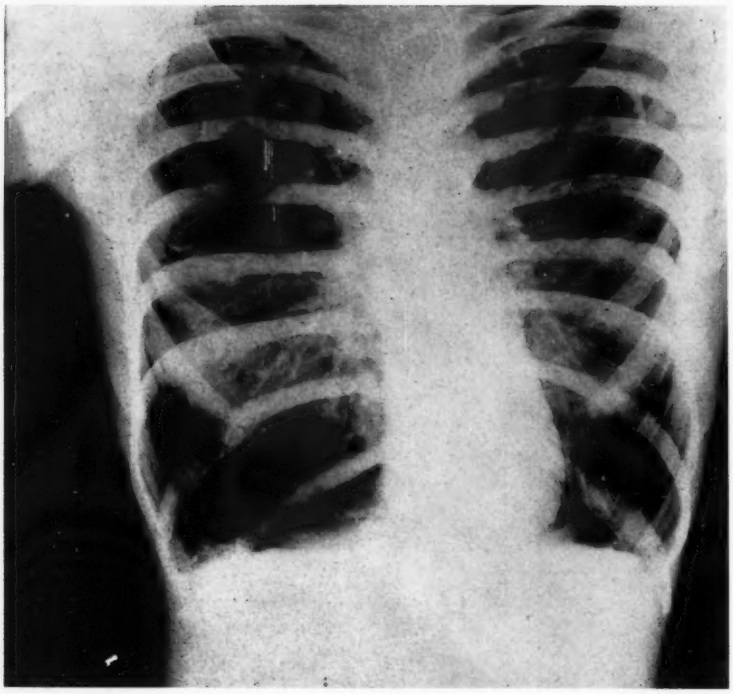
Chronic bronchial asthma with severe emphysema. Note increased antero-posterior diameter.

Bronchial asthma with emphysema.

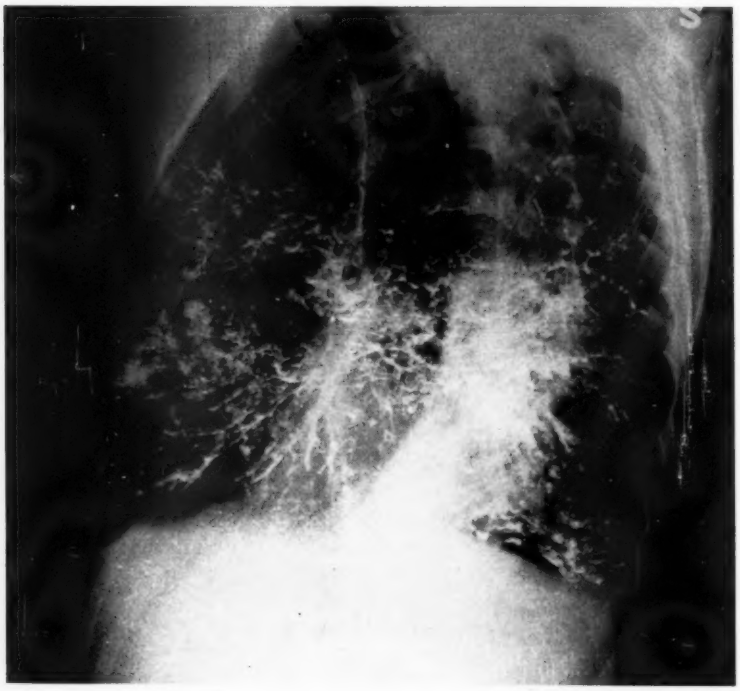


Bronchial asthma (chronic) with emphysema. Note increased antero-posterior diameter.

Large nasal polyps in an asthmatic patient. Removal of polyps frequently relieves asthmatic symptoms.



Severe chronic asthma with marked emphysema: ribs almost horizontal, wide intercostal spaces, small heart, depressed diaphragm (practically no movement on fluoroscopy). Also note three small areas spontaneous pneumothorax due to rupture emphysematous blebs. Emaciated woman, 28, asthma since infancy, weight 70 lbs. on admission to hospital. Marked improvement with gain to 104 when given high caloric diet and injections of adrenal cortex plus extra salt. Positive skin tests for molds, pollens, house dust. Good response to continuous aminophylline intravenous therapy.



R. P. Man, 32, chronic asthma, hay fever, bronchiectasis (note cavities in lower left lobe, with slight involvement right lower lobe). Lobectomy (left lower lobe) at Wesley Memorial Hospital, May 1946, because of persistent malnutrition, cough, showers of moist râles and frequent bouts of pneumonitis with fever, chills, hemoptysis. Excellent results. Left hospital in two weeks and has gained about 20 pounds. Lungs now almost clear. Continues injections of pollen, mold, and house dust extracts.

40-year-old woman with chronic asthma and moderate emphysema. Skin tests practically negative and response to treatment fair only. Note anatomy of trachea, bronchi and smaller branches as shown by instillation of iodized oil. Bronchiectasis minimal. Fluoroscopy: poor expansion diaphragm.

81-year-old woman entered hospital with diagnosis of bronchial asthma, but re-examination revealed inspiratory (stridorous) wheezing rather than expiratory, and dullness and decreased breath sounds below right clavicle. No apparent goiter but x-ray showed large mass which pressed against esophagus, trachea and right main bronchus. Diagnosis: substernal thyroid (nontoxic). Removal urged but patient refused. Wheezing, dyspnea and orthopnea continued with death in about four months. Autopsy: huge substernal goiter with much colloid. Terminal bronchopneumonia. Substernal goiter not infrequent cause of wheezing and is mistaken for asthma.

(Above left) Giant ragweed growing to height of 6-7 feet. Pollen is carried by wind. Very important cause of hay fever and asthma in August and September.

(Above right) A patch of pigweed growing in a vacant lot. The pollen of this amaranth may be a factor in late summer hay fever.

(Left) Goldenrod. Its pollen is carried by insects and is therefore of little importance as a cause of hay fever and asthma.

(Below left) Flower of the hard maple tree. Its pollen is important as a cause of spring hay fever.

(Below center) Flowering catkin of poplar tree. Its pollen may cause spring hay fever.

(Below right) Flowers of the elm tree. The pollen is shed in large amounts in the spring and has high allergenic toxicity.

(Above left) Typical chest of boy with bronchial asthma since infancy. Sensitive to numerous allergens.

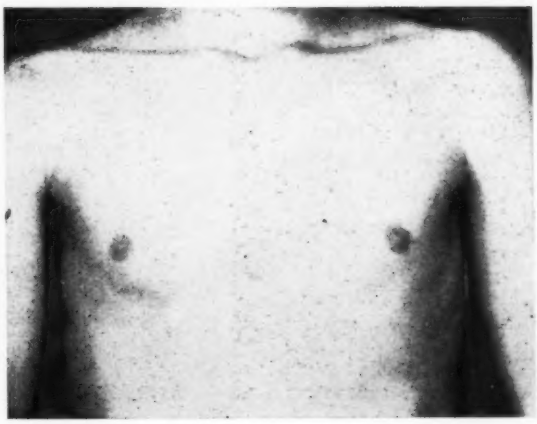
(Above right) Chest of same patient showing characteristic pigeon-breasted deformity due to chronic asthma and resultant emphysema.

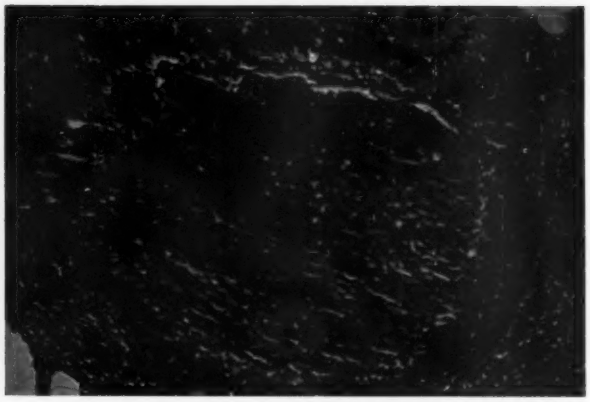
(Right) Bronchial asthma with pronounced barrel-chest characteristic of older emphysematous patients.

(Far right) Boy, 15, chronic asthma with emphysema. Responded to avoidance and hyposensitization.

(Below left) Asthmatic emphysema and barrel-chest deformity of an older boy as contrasted with pigeon-breasted enlargement of chest in younger patients.

(Below right) Same boy. Antero-posterior view.





(Above) Microscopic study of lung of one-year-old patient who died 17 hours after onset attack asthma: bronchus obstructed, emphysema, eosinophilic infiltration of tissues.

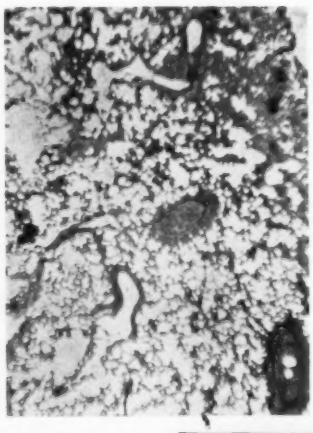
(Middle row left) Marked emphysema of lungs in an asthmatic man who died during an attack. Note the large air sacs and the tearing of partitions between them.

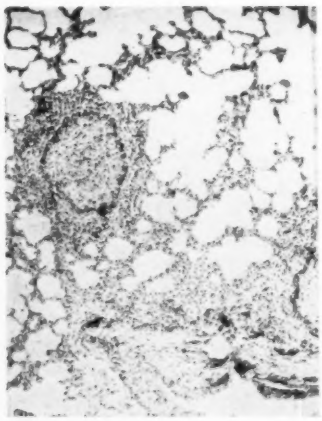
(Middle row center) Bronchial asthma, emphysema, mucous plugs. From lung of a one-year-old infant who died 17 hours after onset of attack of asthma.

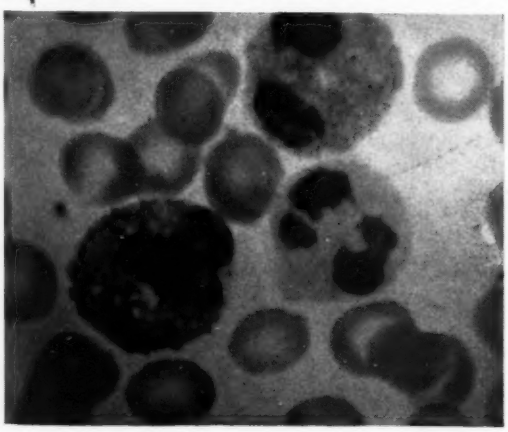
(Middle row right) Plugged bronchus and marked emphysema; eosinophils numerous in the plug and in the walls of the bronchus. From lung of one-year-old infant who died 17 hours after onset of attack of bronchial asthma.

(Bottom row left) Bronchiole from same asthmatic patient. Note mucous plug, with incomplete obstruction.

(Bottom row right) Blood eosinophilia from asthmatic patient; note two eosinophils and one neutrophil in the smear.







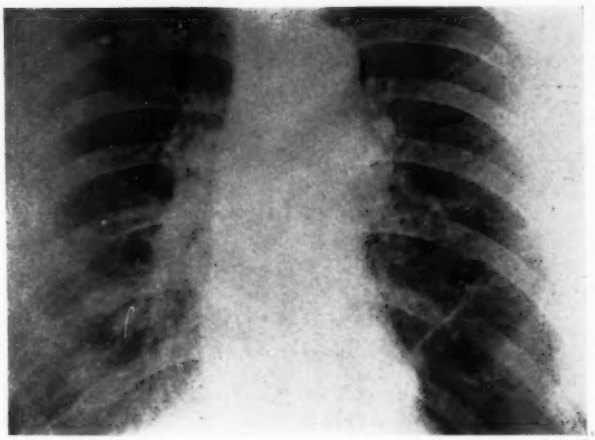
(Middle row left) Higher magnification (x315) of section of same bronchiole showing mucous plug with severe inflammation and many eosinophils.

(Middle row center) Bronchiole from same asthmatic patient. Note complete obstruction. Many eosinophils.

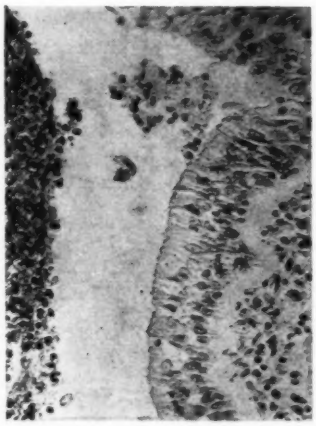
(Middle row right) Higher magnification of same baby's lung; obstruction bronchiole by mucous plug; emphysema associated.

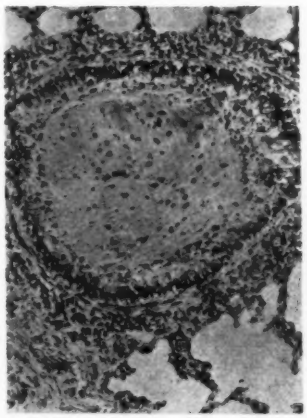
(Bottom row left) Nasal smear from patient with allergic rhinitis, showing numerous eosinophils.

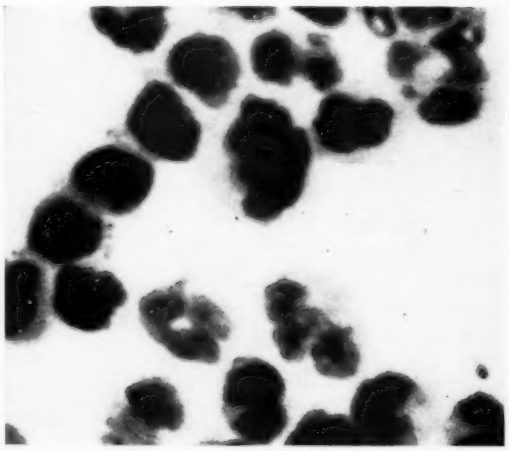
(Bottom row right) Section of middle turbinate; note eosinophilia. (Courtesy, F. K. Hansel.)

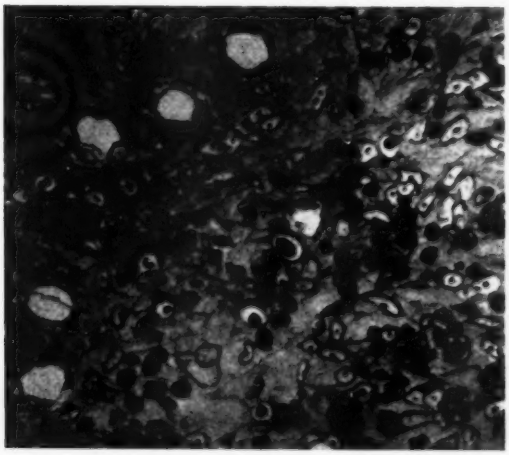


(Above) Bronchial asthma, complicated by emphysema and large bleb in lower lobe. Danger of rupture of bleb with resultant spontaneous pneumothorax.









Congenital Hemolytic Icterus

REPORT OF CASE ASSOCIATED WITH SEVERE COLITIS CURED BY SPLENECTOMY

STEPHEN C. STAHLNECKER*

PHILADELPHIA, PENNSYLVANIA

CONGENITAL hemolytic icterus is a familial malady which was first clearly described by Minkowski[1] at the turn of the century. Its symptomatology is variable and its diagnosis is sometimes difficult, but because of the very dramatic cure effected by splenectomy, early recognition is of the utmost importance.

PATHOLOGIC PHYSIOLOGY

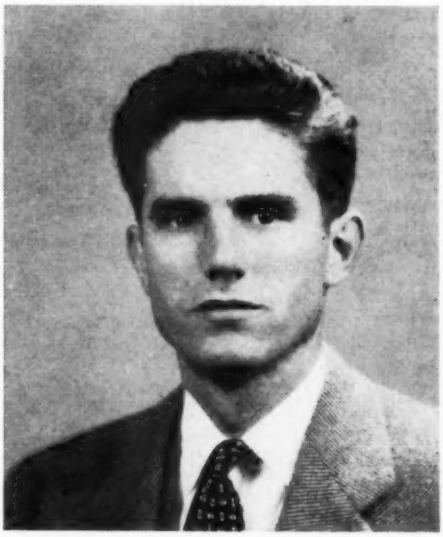
The etiology remains undetermined. There appear to be two possibilities: first, a defective erythrogenesis, resulting in a small, globular, hyperchromic, red blood cell, the spherocyte;[26] second, abnormal erythrocytes may be formed by some unknown agent acting on originally normal red cells. The patient's spleen destroys these abnormal red cells.[22] His bone marrow is continually overstimulated by the demand to replace these destroyed cells. He is in a precarious state of hemolytopoietic balance, as pointed out by Doan.[2] If his marrow cannot maintain the pace, he becomes anemic. His excretory system may be overloaded by the excessive hemoglobin breakdown. He becomes icteric or may develop pigment stones in his biliary tract. His spleen may become greatly enlarged. He is always subject to sudden hemolytic crisis at any time from early childhood to old age.[24] These crises may be fatal, they may spontaneously remit, or they may be cured and subsequently prevented by splenectomy.

From the service of Edward L. Bortz, M.D., Lankenau Hospital, Philadelphia.

DIAGNOSIS

The presenting symptoms in any particular case vary with the severity of the anemia and the degree of splenomegaly, or, as Chauffard[10] noted, the patient may be more icteric than sick. Occasionally the initial picture may be that of biliary colic.

The diagnosis rests upon the discovery of a microcytic, spherocytic, hyperchromic anemia, a well-marked reticulocytosis, splenomegaly, and icterus. It is essential to demonstrate that these spherocytic cells are abnormally susceptible to hemolysis by hypotonic salt solution, as Chauffard first showed in 1907.[10] A familial history of the disease is exceedingly helpful in reaching a diagnosis but cannot always be obtained. The following case is presented as illustrating the difficulties that may be encountered in diagnosis; it is also of interest because of the unusual association with a severe colitis.



STEPHEN C. STAHLNECKER

CASE REPORT

First admission—J. M., a 30-year-old woman, born in this country of Italian parents, was admitted to the hospital, complaining of shortness of breath of two weeks' duration. Two years prior to admission she had begun to have severe occipital headaches of two to three days' duration at the time of her menstrual periods. The headaches had grown progressively worse. Two weeks prior to admission she had first noticed dyspnea and pounding in the chest when walking uphill or climbing stairs.

For the last fifteen years the patient had been working in the food preparation department of a chain store eight hours daily and, in addition, had been doing all the cooking and most of the washing and cleaning for a family of six in her nine-room home. A diet survey revealed that she had eaten practically no meat since childhood. At the ages of 18, 22, and 26 she had had irregular treatment with liver and iron for anemia, but she had not continued the treatments because she had felt well. She had never noticed any jaundice. Her menses had begun at the age of 16. They had been regular but scanty, and she had missed the period that was due two weeks before admission. Six weeks prior to admission she had been married and had quit her job. She had been given one injection of 2 cc. of crude liver by her referring physician two weeks before hospitalization and had been taking Lextron capsules and Feosol pills daily while awaiting admission.

Family history revealed that one sister had slight anemia all her life and another sister had had severe anemia during a pregnancy. Her mother had died at 51 of carcinoma of the stomach. Her father and three other siblings were examined. They had no anemia nor splenomegaly, and their red blood cell fragility was found to be normal.

On physical examination the patient was found to be extremely pale. She was not jaundiced. She weighed 122 pounds. Her blood pressure was 100 systolic, 60 diastolic. There was a loud, blowing, systolic murmur audible all over the precordium. The spleen was not palpable. There was no evidence of neurologic abnormalities.

Our studies showed a red blood count of 1,220,000 with 4.3 gm. (28 per cent) of hemoglobin. There was a reticulocytosis of 42 per cent. Hematocrit was 11. Our calculations revealed a mean corpuscular volume of 123 cubic micra (normal, 87 ± 5), a mean corpuscular hemoglobin of 35 micromicrograms (normal, 29 ± 2), a volume index of 1.4, and a color index of 1.1. There were 330,000 platelets per c.mm. Coagulation and bleeding times were normal.

A red cell fragility test showed hemolysis beginning at 0.45 and complete at 0.35 per cent salt solution (control, 0.45 to 0.35 per cent). The blood smear was reported as showing considerable anisocytosis, macrocytosis, and polychromasia, compatible with a diagnosis of pernicious anemia. However, a gastric analysis showed 10 units of free acid and 40 units total acidity. The x-ray examination of the chest and gastrointestinal tract revealed no abnormalities.

The basal metabolic rate was plus 21 per cent. An electrocardiograph was normal.

She was given 1 cc. of reticulogen daily for ten days with slight improvement in her anemia. After two weeks the patient refused further studies and treatment and left the hospital against advice. She was signed out as anemia, type undetermined.

Second admission—Three weeks later she was readmitted to the hospital. The physical examination did not show any significant changes, except the loss of 6 pounds. She stated that she had had a severe watery diarrhea with from 10 to 12 stools daily for the six days prior to her second admission.

At the time of this second admission the patient's red blood count was 670,000 with 20 per cent hemoglobin. The red cells showed marked anisochromia but practically no poikilocytosis. The white blood count was 33,000 with 67 per cent neutrophils. There was a 46 per cent reticulocytosis. An icterus index was 15. The indirect van den Bergh test was 2 mg. per 100 cc. The red cell fragility test was repeated and showed hemolysis beginning at 0.64 and complete at 0.40 per cent salt solution (control, 0.40 to 0.28 per cent). A smear of the sternal marrow showed a normoblastic type of red cell regeneration together with hyperplasia of the granulocytic series.

She ran an irregularly febrile course with temperature elevations to 104° F. Her profuse diarrhea failed to respond to various medications. She then averaged about 15 stools daily, many of which were grossly bloody. Repeated stool examinations were negative for typhoid, paratyphoid, and dysentery organisms. Neither ova nor parasites could be found. No splenomegaly could be detected on physical examination by many different observers. The spleen could not be visualized by x-ray. At one time the white blood count rose to 50,000, but no leukemic cells were found. The urine urobilinogen was positive in 1/10 dilution. The stool urobilinogen was 50 mg. in twenty-four hours. Repeated tests showed a persistently increased red cell fragility.

On the thirty-fifth hospital day it was decided that splenectomy presented the only hope of cure, despite the absence of splenomegaly and jaundice. She was prepared for operation by daily transfusions for one week, which brought her red cell count to 3,000,000.

At operation the spleen was found to be enlarged. It weighed 400 gm. and measured 14 by 9 by 4.5 cm. There was a tiny accessory spleen. The biliary tract seemed normal. The colon was grossly thickened and strikingly injected throughout. Microscopically, the splenic pulp was uniformly engorged with red cells. The sinusoids varied; many were empty; some were crowded with red cells. There was a large amount of hemosiderin in the macrophages of the pulp and sinusoids.

Following the operation no further transfusions were given. The red cell count slowly rose to 4,000,000, with 78 per cent hemoglobin. The reticulocyte count fell to 1 per cent. The red cell fragility remained increased at approximately the preoperative figures. Her diarrhea slowly subsided over a period of four weeks. At present, one year after operation, she has one or sometimes two stools a day. She has gained 30 pounds. She is well and active.

DISCUSSION

This patient's past history demonstrates once again the futility and danger of treating anemia with liver and iron without making an accurate diagnosis.

Initially, the apparent picture of a macrocytic anemia was confusing. The large cells, of course, were reticulocytes. Actual measurement of the cells showed that approximately 35 per cent were microcytes. As Douthwaite and Waterfield[11] have emphasized, a blood smear which shows extreme variation in the size of erythrocytes without variation in shape, in the presence of a high reticulocytosis, is practically diagnostic of this disease and rules out pernicious anemia in which great variation in shape is seen. Initial confusion with pernicious anemia is so frequently reported that the principal diagnostic features, which will serve to differentiate these two diseases, when the patient has re-

ceived prior treatment with liver, have been summarized in Table 1.

The first test of red cell fragility was normal. As subsequent preoperative and postoperative tests were consistently increased, it is felt that the initial test was probably a misleading error in technic.

In retrospect, the operation was delayed too long because an enlarged spleen could not be detected. Several authors[3, 12] have stressed the fact that the severity of the anemia in a hemolytic crisis bears no relation whatsoever to the size of the spleen.

The patient was given too many transfusions —sixteen in all—before it became apparent that they were unavailing. In this disease every transfusion is an invitation to disaster in the biliary tract.[17] Perhaps the tremendously increased intestinal motility and loss of blood by bowel in this particular case prevented overloading the biliary system.

What was the relation of this patient's severe colitis to her anemia? The anemia appeared first. The colitis disappeared after splenectomy cured her anemia. It is not felt that the association was accidental. The operation was delayed while attempts were made to combat her colitis, but it is now believed that this unusual complication is an even more pressing reason for immediate splenectomy.

TABLE 1

DIFFERENTIAL DIAGNOSTIC FEATURES IN CONGENITAL HEMOLYTIC ICTERUS AND PERNICIOUS ANEMIA AFTER TREATMENT WITH LIVER

DIAGNOSTIC FEATURES	PERNICIOUS ANEMIA	CONGENITAL HEMOLYTIC ICTERUS
Reticulocytosis	5 to 20 per cent	20 to 60 per cent
Marrow smear	Normoblastic	Normoblastic
Peripheral blood smear	Marked poikilocytosis and slight anisochromia	No poikilocytosis and marked anisochromia
Red blood cell fragility	Decreased or normal	Increased
Free gastric acid	Always absent	May be absent
Stool and urine urobilinogen	Increased slightly	Increased greatly

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The Medical Bookman

DIAGNOSIS IN DAILY PRACTICE*

THE PRACTICING physician is primarily responsible for the management of those illnesses which are the major causes of disability and death. He likewise should hold himself accountable for the prompt recognition and handling of the predisabling phases of such diseases in order to prevent more drastic complications." . . . This is the opening paragraph of the preface to this newest of books on differential diagnosis in medical practice and it states compactly the purpose for which it was written.

Most authorities agree that the decline of the general practitioner, the family doctor of revered memory, is the greatest disaster in the history of modern medicine. But they also agree that the practitioner of tomorrow must be a different person from his often inadequately educated predecessor of the days of simpler living.

To be an effective doctor today, a wide general knowledge is demanded, but medical knowledge has become so complex that no doctor can hope to be familiar with all phases of it. What he should know is how to obtain the information necessary to make an early diagnosis, and with enough certainty to treat the patient before the disease has progressed too far, or be able to realize the need for specialist care when it arises. When more general physicians possess that knowledge, less patients will go to specialists in the first place, and medicine will become more efficient and less expensive.

One way to accomplish this aim is, of course, to make every doctor train himself to the competence of an internist, something which is not likely to happen. The other way is to streamline diagnostic studies and make easily available the detailed knowledge which an internist should possess. This end can well be accomplished by Dr. White's and Dr. Geshickter's book and, as such, it is an important contribution to medical practice.

While there are something more than 2,000 recognized disease entities, thus immeasurably complicating the diagnosis of obscure symptoms, tables of mortality and morbidity in the United States show that only about 200 of them constitute 98 per cent of the conditions requiring the attention of physicians. Therefore, the authors state: "In order to determine the most valuable diagnostic procedures for routine use, statistical surveys of the leading causes of death and disability in the United States have been utilized. Abnormalities which are essential to the recognition of these prevalent diseases have been used as criteria for selecting the component steps of the examination. Only the most simple and reliable means of eliciting such abnormalities have been chosen. The object has been to arrive at a routine which is comprehensive but sufficiently brief to be employed in everyday practice. In the authors' hands, with technical help for the six laboratory procedures, the examination has been performed routinely within a period of twenty minutes."

A major departure in this book is the presence of two tables, conveniently placed on the inside of the front and back covers. The front table lists the 200 most common disease states, keyed to the text pages covering their symptoms. Inside the back pages is a list of major abnormalities usually encountered in the medical study, again keyed to appropriate tables in the text which list the disease

*Diagnosis in Daily Practice, An Office Routine Based on the Incidence of Various Diseases. By Benjamin V. White, M.D., and Charles F. Geshickter, M.D. Philadelphia: J. B. Lippincott Company, 1947. Price: $15.00.

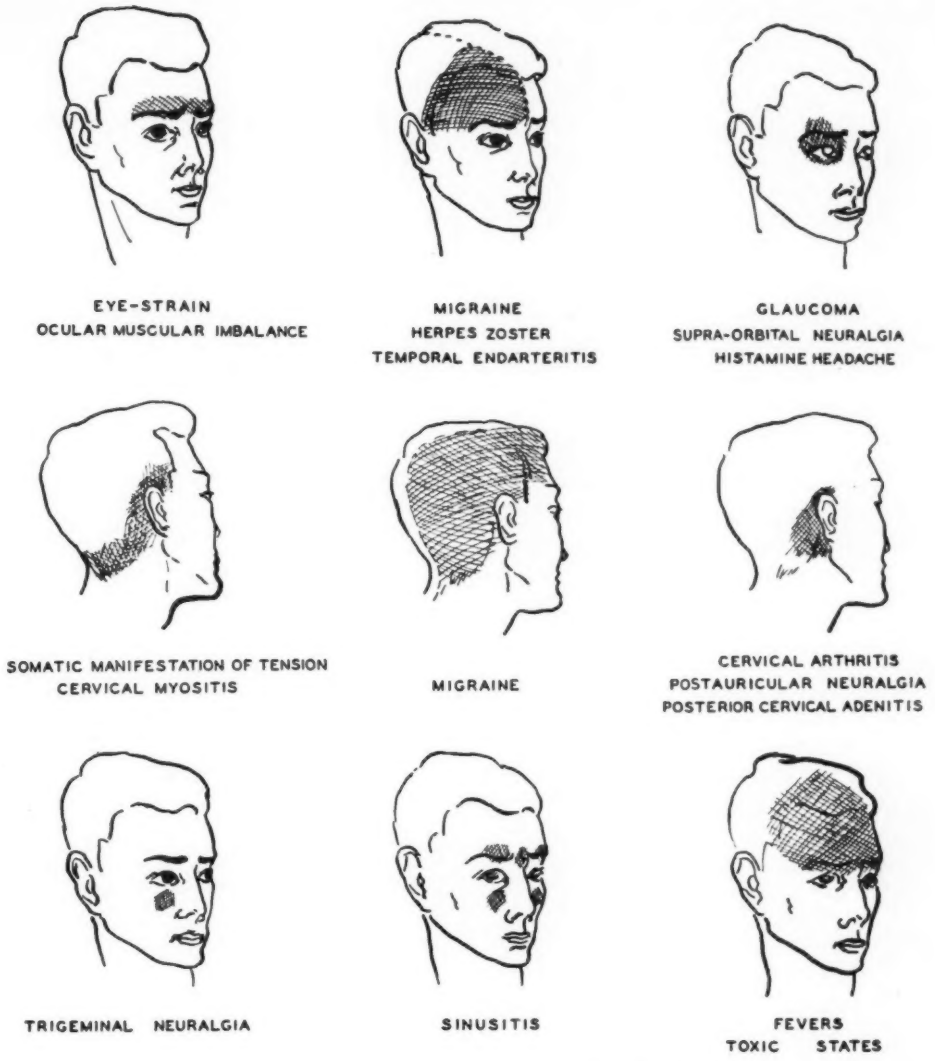


Figure 29. Common sites and leading causes of headache.

conditions in which the corresponding symptoms are present. The reader thus has available at a glance an index of both symptoms and diseases.

The most striking contribution of *Diagnosis In Daily Practice* is the concept of "presymptomatic medicine." As the authors state: "Presymptomatic medicine lies midway between preventive medicine and therapeutic medicine. It aims at the recog-

nition or discovery of abnormalities of structure or function which may form the basis of subsequent disability or disease which cannot be eliminated by existing sanitation or hygienic measures. It is a phase of medicine which could not have existed a century ago, but has been made possible by newly acquired knowledge of the precursors or early stages of disease whose association with the fully developed form was not previously recognized.

"One of the reasons why statistical data regarding the major diseases has been neglected by the medical profession is found in the clinical approach. The practitioner must be prepared to discover and treat the ailment of the individual, regardless of its rarity, and for this reason, medical schools have laid a disproportionate emphasis upon rare diseases or those which present unusual diagnostic difficulties. In a standard textbook of medicine the major groups of diseases which are responsible for 98 per cent of the illness in the United States receive only 40 per cent of the space, and in a standard work on laboratory diagnosis the essential laboratory procedures which are applicable to the routine diagnosis of this major group comprise less than 5 per cent of the text. Thus in his medical education the future practitioner spends most of his time learning to diagnose those conditions which he will see the least number of times. The apparent assumption is that he will be forced to learn the common conditions from personal experience. The late stages in which most of the fatal diseases are diagnosed prove that this is an unwarranted assumption."

The "Diagnostic Survey," as described above, consists of: "(1) taking the past history and that of the present illness, (2) performing the physical examination, and (3) conducting an essential group of laboratory determinations."

"A survey of the approximately 200 diseases which are responsible for 98 per cent of the illness in the United States reveals that there are 16 common symptoms, 23 leading physical abnormalities, and 6 essential laboratory findings which will serve as keys to their differential diagnosis. It is entirely practical to construct the diagnostic survey around this list, since the presence or absence of any of the major diseases can be determined from them, provided a limited number of additional procedures are carried out when indicated to confirm the diagnosis thus arrived at."

Going still further, the authors list in order of their importance in causing morbidity, eight major "etiologic disease groups." These are: "(1) susceptibility to *infection with microorganisms,* (2) *degenerative changes,* (3) exposure to *trauma or adverse conditions,* (4) *metabolic and nutritional disturbances,* (5) *allergic response,* (6) *inadequacy of the adaptive function of the personality,* (7) *disturbances in the regenerative capacity of component tissues,* and (8) *congenital or acquired anomalies.*"

In the matter of history taking, always the most important part of a diagnostic survey, the authors consider first the "etiologic history," which seeks the following abnormalities: "weakness; loss or gain of weight; a discharge of blood or pus; fever, chills, or sweats; uneasiness or worry; inability to get along with others."

Next is the "regional history" which elicits the following abnormalities: "headache; fainting, coma, or convulsions; earache or tinnitus; sneezing or nasal drip; sore throat; cough or shortness of breath; chest or precordial pain; dyspepsia or indigestion; change of bowel habits; cramps or abdominal soreness; menstrual disturbances; frequency or nocturia; lameness or backache; itching or rash."

Two tables then correlate symptoms and findings with regional and etiologic significance, locating them with relationship to the organs involved.

The examination procedures of the routine diagnostic survey are carried out according to a definite schedule as listed. With the complexity of modern instruments of precision, it is encouraging that the authors have placed emphasis once again upon the fundamental portions of the examination which can be carried out with little equipment except the senses of the physician. General inspection, for example, largely a lost art, should elicit the presence or the absence of: "discolored or altered complexion; cutaneous sores or blemishes; stiffness, impaired motion or posture; hoarseness; unsteadiness, ataxia, tremors, or twitches; paralysis; vasomotor instability."

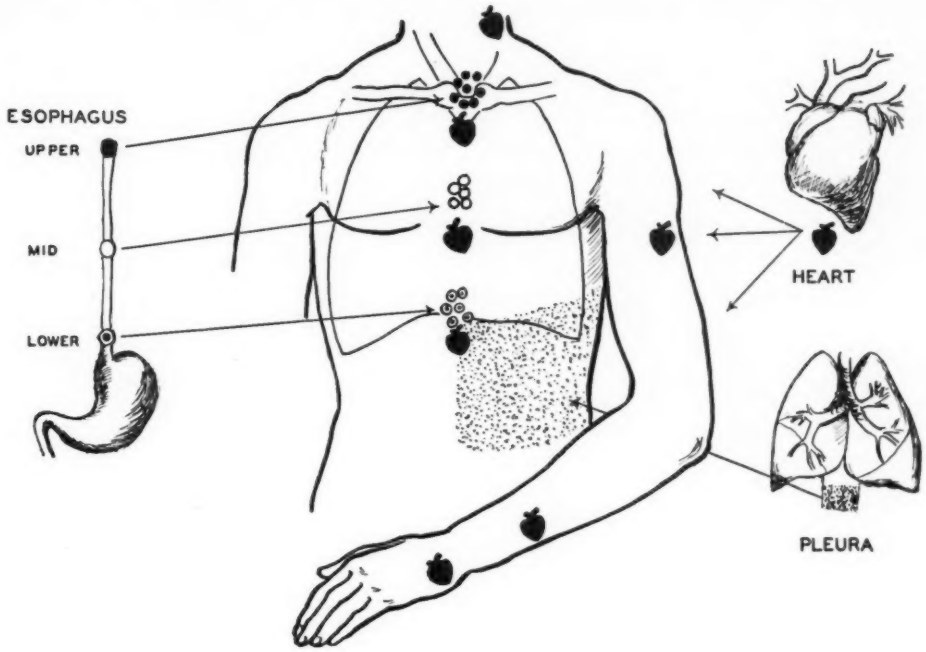


Figure 30. Thoracic regions to which cardiac, pleural and digestive pain may be referred.

Next the authors point out that: "Through the use of simple office implements, such as scales, blood pressure apparatus, stethoscope, a tongue depressor, and a good artificial light, he (the physician) is able to establish or rule out the following abnormalities: fever, loss or gain of weight; pulse or blood pressure variations; cardiac murmurs; dental abnormalities; inflamed or abnormal mucous membranes; râles, rubs, or squeaks (at the lung bases or over the precordium)."

Palpation of the neck, abdomen, and extremities notes: "masses or tenderness; edema; impaired motion or posture not noted on inspection; vascular abnormalities."

Pelvic and rectal examination yields data on: "inflamed or abnormal mucous membranes; masses or tenderness; displaced or relaxed structures."

The neurologic examination, very much simplified, brings out: "hyperreflexia or hyporeflexia; paralysis, defective vision; defective hearing." A simple psychiatric examination completes the survey with information relative to: "retarded, accelerated or bizarre animation; abnormal emotional response; fixed ideas; suspiciousness or spread of meaning; forgetfulness or disorientation."

The six laboratory procedures included in the routine diagnostic survey are: "routine examination of the urine; hemoglobin concentration of the blood; blood sedimentation rate; Mazzini serologic reaction for syphilis; occult blood in fecal material, obtained on glove by rectal examination; x-ray examination of the chest."

With the information of the survey at hand, the diagnostician can now refer to an ingenious chart

included in the book which channels positive findings to the correct disease category, and is then cross indexed to descriptions of individual diseases to be used as a final check.

The authors emphasize particularly one side of the diagnostic study which has heretofore been generally neglected, evaluation of the influence of personality upon physical symptoms. The findings of psychosomatic studies show more and more the importance of these factors. Nor is an emotional evaluation very difficult to obtain, as the authors point out, for "the ability to get along with others at home, at work, or in games or other forms of social intercourse is one of the most reliable indications of a normal personality." A simple question as to how the patient liked school will often give the clue to serious personality disturbances. Another important symptom is uneasiness or worry. These of course occur in normal individuals, but are usually not unduly prolonged. When they are, they usually mean a fundamentally unstable personality, as the authors point out, and such tension is manifested by a fairly definite physical picture which can usually be recognized.

The whole of Part II of *Diagnosis In Daily Practice* is concerned with the importance of individual symptoms in arriving at a diagnosis, including the differentiation of the several disease states presenting each symptom. Headache, for example, is listed as a symptom referable to the head, along with "fainting, coma or convulsions, and earache." It is further divided into extracranial and intracranial headache. Extracranial causes are: "optic headache, sinus headache, and cervical headache," each of which is described in full with diagnostic implications. Under intracranial headache is listed: "headache of intracranial traction or displacement; histamine and fever headaches; migraine headaches; hypertensive headache; and neurotic headache."

Under "Cardiorespiratory Symptoms," as a further example of the way in which etiologic factors are determined from symptoms, we find a discussion of precordial pain:

"Because of the danger in borderline psychoneurotic patients of establishing hypochondriacal tendencies referred to the heart, these data should be acquired as far as possible from the history volunteered by the patient. In general, when substernal or precordial pain occurs in paroxysms the differential diagnosis lies between cardiovascular disease, somatic manifestations of tension, and digestive disorders; when it is chronic or persistent, one thinks of a mediastinal mass."

Part III is concerned with "Diagnostic Abnormalities of Disease: Physical Findings." Here are discussed the various findings of the physical examination. Of inspection the authors say: "The examination of the patient should bring to light objective findings regardless of whether or not their presence or significance has attracted the attention of the patient. It is often the disclosure of apparently insignificant changes, such as petechial hemorrhages of the skin or collateral circulation in the veins of the abdominal wall, which establishes the diagnosis of a major condition such as endocarditis or hepatic cirrhosis. Moreover, the incipient stages of major diseases may thus be recognized and effectively treated before disabling symptoms or irreversible changes have taken place."

In the discussion of skin diseases there are unusually clear charts of location of rashes and their characteristics on several pages of the text, materially aiding the differentiation of these conditions for the practitioner who is not always familiar with them. There are also several excellent plates in color. Other charts of external deformities of diagnostic significance, such as those of the hands, are extremely valuable.

Throughout this book, the proper place of the personality as a controlling factor in much of the symptomatology and complaints of human illness is stressed. Part III closes with the discussion of the psychiatric examination in which the authors say: "An evaluation of the behavior and personality of the patient during routine examinations to rule out psychiatric abnormalities must be accomplished by methods which are brief, unobtrusive, and relatively reliable in the hands of the practitioner who is without special training in psychiatry." An entire chapter is devoted to the psychiatric history and examination, with an evaluation of findings.

Part IV deals with the six routine laboratory examinations. Part V is concerned with differential diagnosis of the major disease groups mentioned

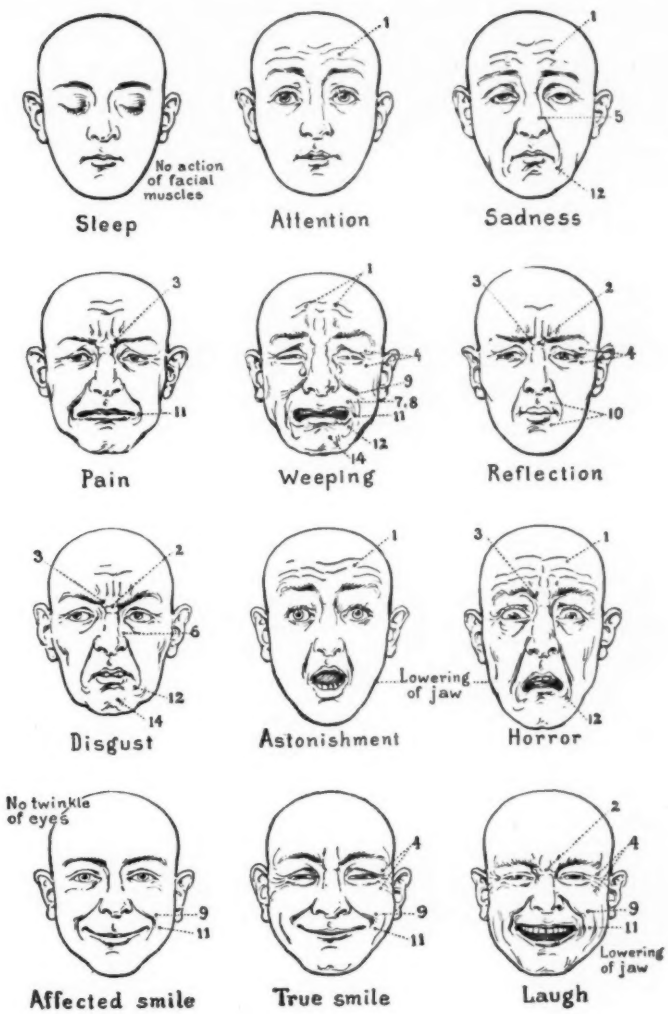


Figure 157. Facial expressions in various emotional states. From time of early infancy the child is influenced by approval or disapproval reflected in his parents' facial expressions. (From Moore, D. T. V.: *Dynamic Psychology*. Ed. 2. Philadelphia: J. B. Lippincott Company.)

earlier in the text. There are concise but complete chapters on all phases of diagnosis in all organ systems. A final chapter details the set-up of an efficiently operating office.

This is a very complete book on physical diagnosis for the general physician, bringing him in readily available form the information necessary to make a certain diagnosis in most of the conditions he will encounter. It is well written, very well organized, and has a fresh and interesting point of view. The survey outlined here will enable the physician to practice better medicine and give his patients more complete care. In this respect it will do much to accomplish an end devoutly to be desired, the elevation of the general practitioner to a high level of competence, establishing him in his key position in the organization of medical practice. For this, if for nothing else, it is a very important and valuable book.

F. G. S.

MEN OF MEDICINE

Man of Awards

DESPITE his youth and a serious handicap, Dr. Dilworth Wayne Woolley, an associate member of the Rockefeller Institute for Medical Research, has already contributed so much to the knowledge of human nutrition that on April 12 in Havana, Cuba, he received from the American Pharmaceutical Manufacturers' Association its highest honor—the Research Award for 1948.

This tribute to the 33-year-old scientist, who is totally blind, was the first by the A.P.M.A. since the Pharmaceutical Medical Research Foundation was organized recently. The Foundation, financed chiefly by the pharmaceutical group, was announced last December by Dr. Morris Fishbein, who described it as the first project ever launched to effect a formal union of the pharmaceutical industry and the medical profession in the service of public health.

Dr. Woolley had scarcely won his doctorate from the University of Wisconsin when he lost his sight nine years ago. Thus, his blindness occurred just as he was crossing the threshold of a career which since then has placed him in the foremost ranks of the nation's physiologists.

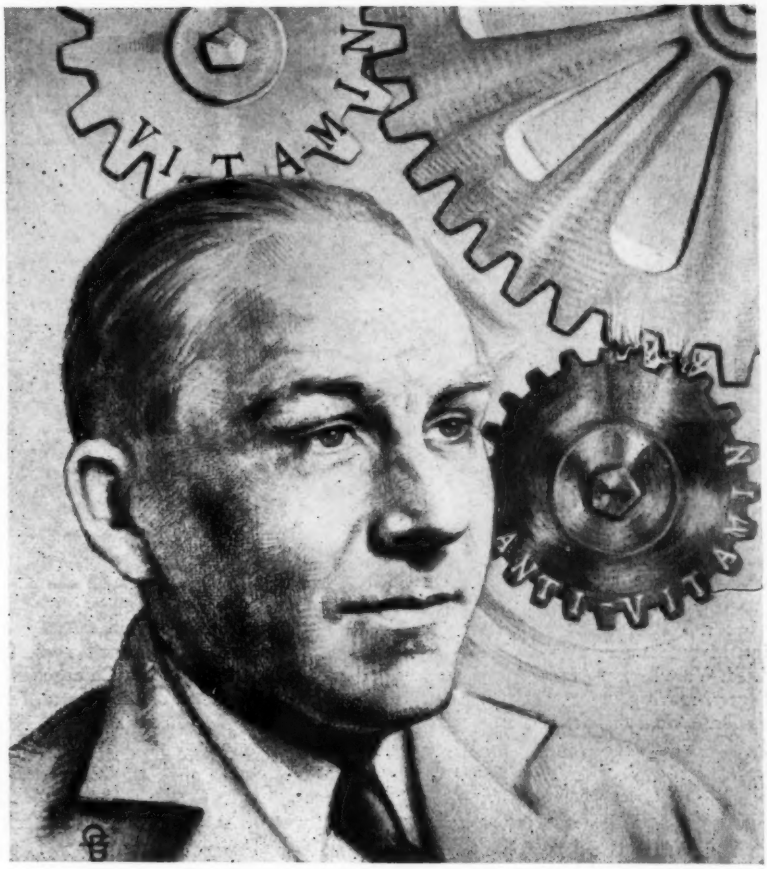
Quietly responsive, yet unable to conceal the scientist's traditional distaste for publicity, Dr. Woolley explained that, even in the earliest days of his blindness, it had never for a moment interrupted the nutritional research which has claimed so much of his time ever since. "I just kept on going," he said laconically.

The Canadian-born scientist explained that he entrusts all laboratory routine to two assistants. These report to him their observations and from step-by-step reports Dr. Woolley controls his experiments, makes his deductions, gauges future procedure, and strikes his conclusions. In this way he pursued the research which has made him one of the nation's few authorities on antimetabolites.

Dr. Woolley was born in Raymond, Alberta, and attended grammar and high schools there. Immediately after graduation from the high school, he began to specialize in the chemical-biology field at the University of Alberta, from which he graduated in 1935. He then enrolled in the graduate school of the University of Wisconsin and while still a student there published with a colleague, reports on two noteworthy experiments. These studies, completed before Dr. Woolley was 21 years old, were entitled, "The Chemistry of Mold Tissue" and "Synthetic Fats, The Preparation of Trinodecylin" respectively, and were published in the Journal of the American Chemical Society.

After Dr. Woolley received his doctorate from the University of Wisconsin in 1938, he spent the summer in England on a traveling fellowship of the sixteenth International Physiological Congress. In 1939 he went to the Rockefeller Institute for Medical Research (physiology) as a Fellow. In 1943 he advanced to an Associate's status at this Institute, and in 1946 became an Associate Member of the Institute.

Mrs. Woolley, the former Janet McCarter, is a bacteriologist and one of her husband's first coauthors. She also received her master's and doctor's degrees at Wisconsin. They met, worked together, and published their joint paper at that university, where the future Mrs. Woolley stayed until 1944. Then a Guggenheim Fellowship brought her to the College of Physicians and Surgeons of Columbia University. In 1945, at the completion of the fellowship, Columbia lost a bacteriologist and Woolley gained a wife who still, in Woolley's words, "shoots a guinea pig now and then" between her household duties.



DILWORTH WAYNE WOOLLEY, PH.D.

(Drawn by Frances O'Brien and reproduced courtesy of *Chemical and Engineering News.*)

IN PRESENTING the Award to Dr. Woolley, Dr. Ernest H. Volwiler, executive vice president of Abbott Laboratories, said:

"The Research Award of the American Pharmaceutical Manufacturers' Association is the highest honor which this organization has to bestow. It is thus a valued privilege to speak of the work of a man who has so outstandingly merited and won this recognition. . . .

"In the years at Wisconsin, while he was a graduate student and for a year thereafter, Dr. Woolley's workmanship in the old laboratory in the basement of the biochemistry building at Madison became a campus legend. Some twenty contributions to the literature ensued, many of them of outstanding importance and all bearing the stamp of deep, original and precise thinking.

"During these years Woolley gravitated between his original job—the chemistry of mold tissue—and the newly discovered factors of the vitamin B-complex, which were exciting the nutritionists on the floors above him. He managed to isolate the amino acids leucine, isoleucine, arginine, histidine and lysine, as well as cyclic choline sulfate from mold tissue of *Aspergillus Sydowi*. He had a hand in the isolation and characterization of nicotinic acid amide as the anti-black tongue factor and the synthesis of many compounds of related nature.

Dr. Dilworth Wayne Woolley (in dark suit) receiving the Research Award of the American Pharmaceutical Manufacturers' Association at its convention in Havana, Cuba, April 1948. Presenting the award is Dr. E. H. Volwiler, executive vice president, Abbott Laboratories, North Chicago, Ill. At the far right is James L. Rogers, retiring president of the Association and also president of the Central Pharmacal Co., Seymour, Ind. To Dr. Woolley's left is Mrs. Woolley.

He also isolated uracil from liver. Possibly his most unique and imaginative contribution while at Wisconsin, however, was his partial synthesis of pantothenic acid before the nature of this compound was even known.

"Woolley knew from the work of Williams' group at Texas that beta-alanine made up part of the molecule of the active compound and had deduced certain knowledge about the remainder of the molecule. He proceeded to acid hydrolyze a concentrate of material known to be active for chicks to completely destroy the activity. He then treated the inactive material, which appeared as just a dark brown smear, with sulfonyl chloride hoping to form an acyl chloride of the unknown fragment. He coupled this with synthetic beta-alanine. His hunch was right and he obtained again an active compound. This work helped open the way to characterization of pantothenic acid, even though the compound was never isolated from natural sources.

"On going to Rockefeller Institute in 1939, Woolley entered into work both with various microbial strains and with rats and mice. He found inositol to be a dietary requirement for mice and used microorganisms to assay for it in foods. He found a new factor for hemolytic streptococci and identified it with a factor required for the best growth of young rats—and called it strepogenin. He determined that vitamin K is a growth factor for Johne's bacillus, a study carried out with Miss Janet McCarter, while still in Madison. This experiment is noteworthy. The research team of Woolley and McCarter apparently cooperated very well and it wasn't long after Woolley went to New York that he returned to Madison to marry Miss McCarter.

"Characteristic of Woolley's thoroughness was

his follow through on inositol to show it as a constituent of a brain phosphatide (with Folch), and his isolation of lipositol, a new inositol-containing phospholipid of soy beans.

"Work with the enzyme in raw fish which destroys thiamine, and with avidin, the factor in egg-white which binds biotin, paved the way for one of Woolley's major fields of contributions to research thinking—the concept of vitamin antagonists. In rapid order Woolley developed antimetabolites for thiamine (pyrithiamine), ascorbic acid (glucoascorbic acid), nicotinic acid (3-acetyl pyridine), and vitamin K (2,3-dichloro, 4-naphthoquinone) to name only part of the list. These compounds were not only synthesized but were tested critically by Woolley, during which time he wrote four major reviews on the subject.

"The possibility for study of vitamin function is amazingly enhanced by the availability of these interesting compounds which compete with the vitamins for position in the enzyme molecule, and thereby block normal body functions. This method provides the most rational approach to the development of new chemotherapeutic agents. Woolley's work, together with his lucid and provocative writings, have had great impact in this field.

"It has been said, 'It is the intuition of unity amid diversity which impels research.' Woolley's bringing together of biochemistry, microbiology, nutrition, and organic chemistry on common grounds has been truly remarkable in providing tools and technics for research which has made for unity in our knowledge of all biology.

"Dr. Woolley, you began as a young man to add to our fund of scientific knowledge, and your contributions have risen at an accelerated rate. You have explored and solved some of our most difficult and basic problems related to nutrition and growth. It is most appropriate that this Association, dedicated to the betterment of human health, should honor itself by bestowing upon you this annual Research Award."

SPEAKING on "The Development and Uses of Antimetabolites," Dr. Woolley described several chemical compounds which are very closely related in structure to various vitamins and hormones. "These compounds or antimetabolites," he said, "have the power to call forth in diverse types of living things the signs of deficiency of the metabolite (i.e., vitamin or hormone) to which they are related in structure. Thus, for example, a specific slight alteration in the molecular constitution of vitamin B_1 or thiamine produces an antithiamine which will cause all the signs of thiamine deficiency when it is fed to animals. Other living things such as bacteria or fungi likewise can be made to develop this vitamin deficiency by giving them this antimetabolite.

"For each of the water-soluble vitamins and for several hormones and other metabolically important compounds, series of such drugs have been produced which are antagonistic to the metabolite in question.

"The mechanism by means of which these new drugs are able to produce their specific effects is viewed as a competition between the drug and the metabolite for a specific protein in the organism. Grossly, it may be likened to the introduction of a plugged nickel into a slot machine, or to the insertion of a slightly misfit key into a lock. The misfit key enters the keyhole readily but cannot quite turn the lock, and at the same time prevents the proper key from doing so.

"The knowledge gained by use of these antimetabolites has enabled the experimenter to develop new kinds of pharmacologic agents which have properties different from existing drugs. It has also allowed the successful prediction of the first members of new series of pharmacological agents; these have powers not possessed by existing drugs. At the same time an insight into the manner in which some drugs produce their effects on living things has been gained." Dr. Woolley discussed a few examples to show how these principles have been applied in experimental models and expressed the hope that these models will be of use in the future development of pharmacology and biochemistry.

In addition to the A.P.M.A. award, Dr. Woolley received an Eli Lilly award in 1940 for work in immunology and bacteriology, has been honored with the Bronze Medal from the Society of American Bacteriologists and the Mead Johnson Award in Nutrition, and will be presented with the Eli Lilly Award in Biochemistry at the 1948 fall meeting of the American Chemical Society.

EDITORIALS

RADIATION AND THE GENERAL PHYSICIAN

It is now more than fifty years since the discovery of the biologic effects of roentgen rays and radium and these modalities have now taken their deserved place in the treatment of properly selected benign and malignant lesions. A considerable amount of education is still needed, however, to acquaint those physicians not specializing in radiology with some facts regarding the use of these agents.

It is common knowledge that for the treatment of hematopoietic lesions, such as malignant lymphoma, leukemia, polycythemia, *et cetera,* radiation is the best palliative measure. It is not as generally understood, however, that proper irradiation of other lesions, such as primary carcinoma of the lip, is as good as surgical measures. For the care of the operable metastatic nodes from such a lesion, however, surgery appears to be far superior.

For the metastatic lesion that cannot be removed completely by surgery, a combination of surgical exposure and irradiation by interstitial radium needles or radon seeds with or without supplementary roentgen radiation will give good results in a significant number of cases. It should also be remembered that for malignant lesions of the tongue, buccal mucosa, pharynx, and palate, irradiation is ordinarily better than surgery, especially cases which are advanced.

The use of roentgen rays is also assuming its proper place in the treatment of carefully selected cases of carcinoma of the larynx. With the exception of malignant lymphoma, there is at present no place for the use of radiation curatively in neoplasms of the lungs and gastrointestinal tract. Aside from Wilms' tumor of the kidney, occurring in children, we have no proof that irradiation benefits malignant tumors of the urinary tract, although it still appears justifiable to treat these lesions of the kidney and bladder in the adult preoperatively.

Regarding the genital tract in women, however, the story is different. For about the past thirty years the mainstay in the treatment of carcinoma of the cervix uteri has been a combination of roentgen and radium radiation and with gradual modification in technic, the five year salvage has risen to approximately 50 per cent in large groups of unselected cases.

Recent reports of the results of surgical treatment of the early stages of cervical carcinoma suggest that this method should supersede irradiation in the early and in the moderately advanced cases.

However, the reported results are not superior to those obtained by proper irradiation in comparable groups and there is the disadvantage that because of improper selection of cases many ill-advised operations are being and will be done on patients with advanced carcinoma. Many times the chances of the patient's obtaining a good result are thus materially lessened.

It is important, therefore, that there be a clarification in the thinking relative to the treatment of carcinoma of the cervix and care taken to avoid undermining confidence in irradiation for this condition. Further dissemination of the idea that surgery can supplant irradiation for this disease would be a definite step backwards.

For other malignant lesions of the female genital tract, however, surgery is the mainstay

of treatment, although it appears evident that irradiation is a valuable ancillary method, especially in the treatment of carcinoma of the uterine fundus and of the ovary. For conditions that can be adequately treated by either surgery or irradiation, it is important to remember that good irradiation is always better than poor surgery and that the converse is also true.

Physicians who are not constantly using irradiation or referring patients for this method of treatment are prone to forget that it is a major procedure when used against malignant neoplasms and that sequelae may appear early or late. The erythema, vesiculation, and superficial ulceration that follow intensive treatment of, say carcinoma of the larynx, is not properly considered an "x-ray burn" because that term by popular and legal concept denotes changes due to ignorance or neglect—and these changes will have been produced purposely.

Late roentgen damage may also appear in the form of fracture of the femoral neck, stricture of the bowel, or sloughing of the laryngeal cartilages when they are invaded by neoplasms.

It is hoped that there will be a decreasing tendency on the part of the profession generally to attribute to the irradiation all untoward symptoms which follow this procedure when given by an experienced radiologist. Sequelae are justified, however, when the treatment is given for the implacable foe—cancer. None of these changes should occur when benign lesions are treated.

In order to use roentgen rays and radium intelligently, therefore, an adequate period of specialized training and experience is required.

Fever is rarely a result of irradiation, but nausea is not uncommon when irradiation is given over the abdomen and pelvis. Transient swelling is a common concomitant of irradiation and this must be kept in mind constantly when the treatment is given over an intact cranium or masses which are causing obstruction to the air passages. But all too frequently the nonradiologic physician is prone to attribute to radiation all symptoms which he cannot otherwise easily explain. The writer has seen cases of fever blamed on radiation when the physician *thought* the patient was being treated, but where no radiation had been given and other cases where cutaneous changes due to the repeated application of a hot water bottle were attributed to irradiation and called an "x-ray burn"—when no radiation had been given over the area.

To say, of course, that no unjustified damage is done by radiation would be false, but so is unjustified damage done by poorly advised and poorly performed surgical operations. It is important to remember that each method—radiation and surgery—is important in the treatment of malignant neoplasms, that they are complementary and not competitive, and that an appreciation of the advantage of each in various conditions must be honestly sought by all who care for cancer.

H. D. K.

THE "ALLERGY SEASON"

The transition period from summer to fall has always been a very difficult one for the allergic patient and the allergist.

Among the reasons for this may be included such factors as: the change from an outdoor life to an indoor one; the starting of heater fires, stirring up dust that has been gathering in the pipes and ducts of the furnace all summer; the change of temperature—each day the patient must adjust himself to cool, damp mornings, warm noontime and again cool, damp evenings. Usually, at this time of the year, the first wave of respiratory infection has begun—and this, in addition, adds to the difficulty of the allergic patient.

Also, a great many of these individuals have been through a pollen season during which they have not been too successfully treated. They were under-dosed or over-dosed or had no treatment at all, or were uncooperative in taking proper care of themselves. All of these conditions add to the difficulties of the patient.

Usually this transition period lasts about two weeks. Last year was an extremely difficult one because of its great length. The ragweed pollen season was practically over about September 18. By this time, the pollen count had dropped to less than 25 and everything should have been all right. However, from September 18 to November 15, we experienced the most difficult fall season in twenty years. More severe asthma was seen (Philadelphia) during this period than ever before. Those patients suffering with seasonal or non-seasonal allergic rhinitis were miserable. Patients who had been discharged as cured, who had had no trouble for several years, had a recurrence of their symptoms. Even dermatologic allergies seemed to be aggravated.

Allergists from New York and Boston reported similar experiences.

Perhaps this editorial will be provocative of suggestions that will enable us to deal better with this seasonal difficulty.

H. L. R.

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Leaves from a Doctor's Diary

By Maurice Chideckel

June 1 . . . From young Dr. Govans: "Look, a check for five thousand dollars. From that California man whose girl with bacterial endocarditis and patent ductus arteriosus I successfully treated with penicillin. Now I am going to be married. When we return from our honeymoon I want you to visit us, but come when I am in." Today the couple came back. So did the check.

* * *

June 2 . . . "Raw eggs," I told Mr. Paul Ingle, "have no deleterious effect on people with duodenal ulcer. You have not, what doctors call, an allergic response, hence you need not eliminate raw eggs from your diet. I wanted to tell you this last night when I saw you going out of the movies with your wife." "With my wife," he repeated. "Beautiful woman, isn't she? Now, please, I beg of you, don't tell my wife that you saw me with her. I have special reasons for it. Promise?"

* * *

June 3 . . . The perpetual conflict of loyalties. Grace Kenneth loves Jerome and she also loves Buddie. Jerome is the husband and Buddie is the dog. Buddie is a newcomer. The lady was unconcerned about the various forms of human allergy, atopic or nonatopic, in allergens being atopic, and the emanations from animals, in this case from beloved Buddie, causing Jerome's serious case of asthma.

There lay Buddie and growled, and there sat Jerome and wheezed, wheezed pitifully. "Give or drive the dog away, or hand him over to the dog pound," I advised. "What did you say?" Her eyes spat fire. "Say that again." She was in a furious mood and I lost her as a patient and a friend. I was reminded of a "poem" from *Farm Festivals,* published in 1881:

Careful with fire is a good advice we know;
Careful with words, is ten times doubly so.
Thoughts unexpressed may sometimes fall back dead;
But God himself can't kill them when they're said.

Was this a question that transcends human intelligence? A dog and a husband. Who shall it be? But then something happened. Dog and husband both went out. The husband to breathe, the dog to chase a cat. Then she heard the screeching of wheels and a sudden stop. Grace paled to transparency. She ran to the window. She feared it was the dog who was killed.

It was.

Well, she found cheer in her sister's giving birth to a new baby, the seventh. I told the little boy downstairs that he has a new brother. "Where are you running?" I asked him. "To tell mother," he informed me, "she'll be so glad."

* * *

June 6 . . . It was a turbulent land, that home of Mr. and Mrs. Wheeler, with the two combatants charging in all directions. How deceptively serene the living room and its occupants looked when you entered it. He believed in the standardization of life; she abhorred inertia. He wanted children; in her opinion, there are already too many brats. He viewed all men as equals. Her hatred of foreigners, especially Greeks, was an obsession bordering on the abnormal. She viewed all Greeks as the apple vendor a few blocks away who charged 2 cents for one apple and demanded 5 cents for two. A Greek family of considerable intelligence moved in next door, and her blind intolerance became more vehement.

Today I was hastily summoned to see her. She was the textbook case of hysteria. The emotional conflict translated itself into physical disability. A few hours ago she learned that her mother's present husband was not her father; that her mother's first husband, her real father, now dead, was a Greek. The contractures and epileptic attacks resembled organic lesions. A greater calamity could not have befallen her. To cure her is to remove the cause. How?

Can narrowness be widened? Can senseless prejudices be converted into broad tolerance? Prejudices and animosities against race, religion, foreigners. Incurable as the metastases of malignancy; unconquerable as death. That scourge will never be banished from the earth. Adroitness, persuasion, argumentation, sermons in the churches, lectures in the universities, like the moving finger in Omar Khayyam, will not erase one iota from a darkened brain. How can I eradicate the underlying cause that ages of attempted enlightenment failed, and cure the disease that is prevalent in the cultured and the enlightened?

And as I sat and thought and pondered and reflected, there was a tap on my shoulder. Mr. Khasanowitch wanted a bit of information. The urologist learned that he has five hundred dollars and advised immediate operation on his prostate gland. He wanted to know: "Suppose I would not have five hundred dollars, would I still need to have an operation?"

June 10 . . . Middle-aged celibate colleague Hugh Hill's life became nothing but that of inner emptiness. His thoughts did not lend themselves to rhetorical expression, or to no expression at all. The trained and disciplined temper common, or supposedly common, to all medical practitioners, failed him. He was robbed of his sweetheart, and he brought her over to the robber.

The bad man: aged 46, suffering from the commonest disease transmitted from animal to man, brucellosis. The disease, chronic, was now elusive and difficult to treat. He established the diagnosis by the agglutination test, and he considered it final. The patient, a very wealthy bachelor, after years of ill health, was now wholly incapacitated. Dr. Hill is a poor man and his bride-to-be, Thelma Darling, is no richer. The doctor persuaded the young woman to nurse him twenty-four hours a day, until. Thelma Darling found the helpless man very interesting. I entered the doctor's office as he was reading a little book called *The Psychology of Rumor* in which the authors state that it is impossible to exercise scientific control on genuine rumors.

"Rumor," spoke Dr. Hill, "is meaningless. There is a rumor in the neighborhood that Thelma is infatuated with Austin Kenny, that crippled creature. You know what a monstrous falsehood that is."

Two days later he learned that the rumor was a bodied fact, for Thelma married Mr. Kenny. The epithets the doctor applied to both could be found in no dictionary. Those who have known the pulsing excitement of love will understand the wounds inflicted on brother Hill. But praised be the Lord. In His great and infinite mercy He called His suffering son, Austin, unto Himself, and so liberated Thelma Darling from the bonds of matrimony. Today, yes today, one week after Austin's death, Dr. Hill and nurse Darling became fused into one. "Do you think my nursing hastened his relief?" she spoke and laughed heartily. Could be. Anyhow life for my colleague is no longer empty. It is once more momentous and full of meaning, and of money.

* * *

June 15 . . . No member of the medical profession can be accused of infirmity of mind, or of mind's inactivity. Creative thought is a part of it, and this thought created the unionization idea. Ah, a Doctor's Union. This union will lift the profession out of servility, will eradicate all legitimate grievances, will prevent one doctor's stealing a patient from another doctor, will force the patient to pay his bills, will force the admitting offices in the hospital to do away with favoritism, and many other benefits. And won't we have a host of exciting experiences. If our demands are not granted, we will have a sit-down strike. We will just sit.

What will we demand? That's beside the point. . . . We have union, we must make demands. Shall we join the C.I.O., the A.F.L., or be a separate entity? I propose a separate entity. We must be original. As men of science we cannot, we must not, be content with imitative effort. We must be careful in selecting our officers. No man living is fit to be trusted with unlimited powers. A name? The Association of Physicians and Surgeons of the American Continent sounds impressive. This appellation would include urologists, psychologists, gynecologists, pathologists, cardiologists, allergists, dermatologists, phthisiologists, obstetricians, pediatricians, diagnosticians (no technicians), radiologists, microscopists, ophthalmologists, and what have you.

The status of the stragglers of the vanishing tribe, the general practitioners, like myself, will have to be decided at a special meeting. Shall they be admitted as equals? Preposterous. A motion will be made to change the name from general practitioner to medical brokers. Of course there will be divisions and subdivisions, and so many locals. Division of Gynecology, local No. 898, department of Leukorrhea; Division of Obstetrics, local 3009, department of Sterility in the Female. Same division, local 310, department of Neonatal Salvage. Division of Pediatrics, department of Prevention of Diaper Rash, and so on, and so on, and so more on.

Maybe we can get John Lewis to help us organize a strike, and a sympathy strike from dentists, pharmacists, veterinary surgeons, and chiropractors. A strike, a sit-down strike is always thrilling. Does this appeal to you, brother healer?

Now is there such a thing as stealing a patient? Is the patient your private property, doctor, and hasn't he a right to choose any physician he trusts? Isn't it better to unite, as we did until now, for the advancement of the science of medicine and for the betterment of the human race? Let the patient be your pal, not just a piece of merchandise; establish a human relationship between your patient and yourself, and never, I say never, overcharge. No one can give you what he hasn't got.

The last two sentences I spoke aloud to myself. From the next room came the voice of my redheaded wife: "Look who is talking."

* * *